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EDITA IUSSU SOCIETATUM RADIOLOGICARUM
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VOL. 40 NOVEMBER 1953 FASC. 5

ROENTGEN APPEARANCES IN MECHANICAL RECTAL CONSTIPATION

by

Kristina Ekengren and *Björn Snellman*

Apart from cases such as a tumour, sigmoiditis, volvulus, megacolon &c. the roentgen appearances in constipation have not yet been studied sufficiently to yield information of much practical value. The investigations of WALLDÉN and SNELLMAN have brought to light previously unsuspected causes of intractable constipation. The present paper is intended to give a preliminary report of our experiences in this field, especially from the aspect of the radiologic diagnosis.

Among patients seeking medical attention for constipation there is one group in which certain symptoms are consistently mentioned in response to detailed questions. These patients have difficulty in evacuating the bowels, often irrespective of whether the stools are hard or loose. Some, on straining, feel as if a lump moved down and prevented the contents from being passed. Others state that the stools seem to collect at the side of, or in front of the anus and that pressure from without facilitates defaecation. In many cases, haemorrhoids and anal fissures arise secondarily and aggravate the condition still further.

The ordinary examination by palpation, proctoscopy and radiographic examination of the colon, brings out nothing to account for these symptoms in the majority of cases. This does not, of course, apply to tumours of the internal genital organs and rectum, which often cause similar symptoms. It is only when palpation through the rectum is carried out as the patient is straining that the characteristic signs may be detected (SNELLMAN). These signs, which may occur either separately or con-

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jointly, are of two different kinds, namely, compression of the rectum from without, and distention of its lower part.

Since January 1952 about thirty patients with typical symptoms were examined at the roentgen department of Karolinska Sjukhuset. A special radiographic technique was worked out in the department, bearing in mind the above-mentioned symptoms, especially those suggesting compression of the distal part of the rectum. Most of the patients were women, the majority of them having shown clinical signs of a mechanical hindrance to defaecation.

In the earlier examinations the films were taken with the patient in the erect position, but the technique was soon changed and the films obtained with the patient sitting on a stool with a hole in the middle so that straining would be as effective as possible.

The examination is now carried out in three stages in close succession:

1. with contrast medium in the distal parts of the small intestine only,
2. after filling of the rectum with semi-fluid barium and of the vagina with highly viscous Umbradil,
3. after evacuation of as much of the barium as possible and refilling of the vagina with contrast medium.

Films are taken in lateral and anteroposterior projections with the patient at rest, *i. e.* after the patient has been asked merely to sit still, and with the patient straining as much as possible. During the straining the medium is allowed to flow out freely.

Changes in the mutual internal relations of the pelvic organs are seen best in lateral views, especially in those taken after the rectal ampulla has been nearly emptied of contrast medium. On the other hand, pockets in the sides of the ampulla extending out towards the levators are visualized better in anteroposterior views of a filled rectum.

Owing to the considerable masking, it is not always easy to distinguish between the different parts of the intestine. The films will be more readily interpreted if the first views taken with medium in the small intestine alone are compared with those showing contrast medium in the rectum as well.

Compression of the Rectum from Without

As Walldén (1952) has pointed out, when the normal rectum is palpated during straining it is possible to feel that the anterior rectal wall bulges in a backward and downward direction for a distance of 1—2 cm. This movement is usually more accentuated in patients who

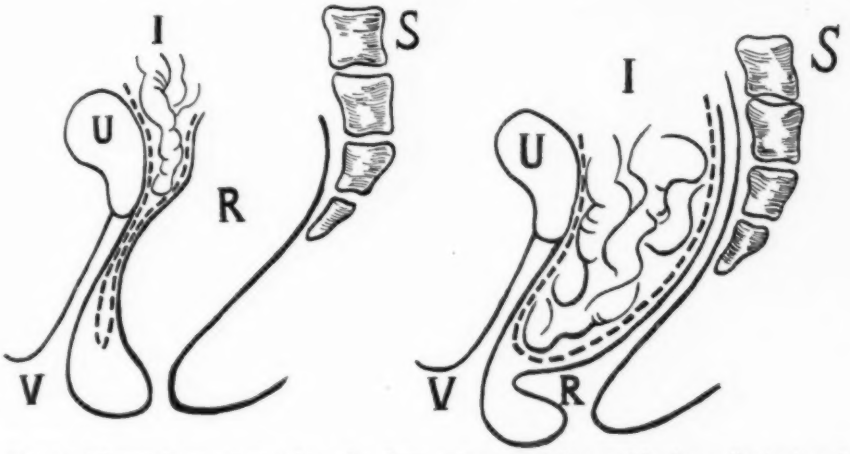


Fig. 1. Schematic representation of a deep rectogenital fossa with the patient at rest, and during straining. I = intestine, R = rectum, S = sacrum, U = uterus, V = vagina.

complain that something is hindering defaecation. The anterior wall is pressed strongly backwards and downwards toward the anal canal by organs situated in front of it while at the same time the lumen of the ampulla becomes compressed. In some cases, the internal orifice of the anal canal is also felt to close up. The organs that can be palpated in this way through the rectal wall are intestinal loops in the peritoneal cavity or a uterus, ptosed as the result of straining.

In the normal adult male, the peritoneal cavity extends down over part of the seminal vesicles but does not reach the prostate. In the adult female, the posterior fornix of the vagina is covered with peritoneum. WALLDÉN has demonstrated that when the rectogenital fossa is unusually deep, portions of the small intestine as well as a part of the sigmoid colon may be pressed down into this space, thus constituting a considerable hindrance to defaecation. Figure 1 (a schematic representation) and figure 2 are illustrations of a case of this type, showing how a large coil of small intestine may be forced down towards the pelvic floor between the rectum and the vagina during straining.

However, in most patients with evacuation difficulties of this type, it proves to be the uterus that is causing displacement of the anterior rectal wall. This can be verified by the observation (cf. SNELLMAN 1951) that when the patient strains down the portio is felt by palpation to be pressing down toward the anal canal. Radiographic examination may also demonstrate pronounced lowering of the uterus in typical cases

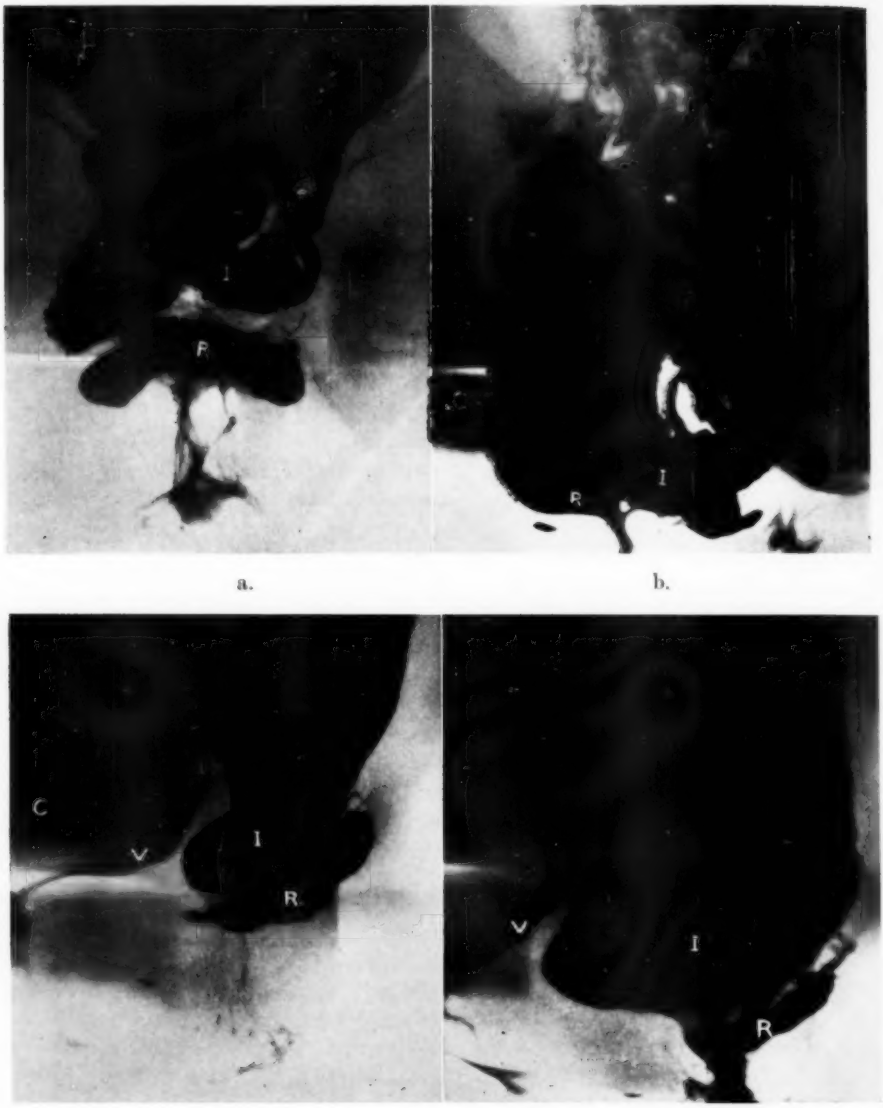


Fig. 2. A 55-year old woman with a deep rectogenital fossa. a) and b) Anteroposterior views with the patient at rest, and during straining. c) and d) Lateral views with the patient at rest, and during straining. All views taken after evacuation of the ampulla. During straining the rectum becomes compressed by the small intestine, which forms a large enterocele in the deep rectogenital fossa. C = chair.

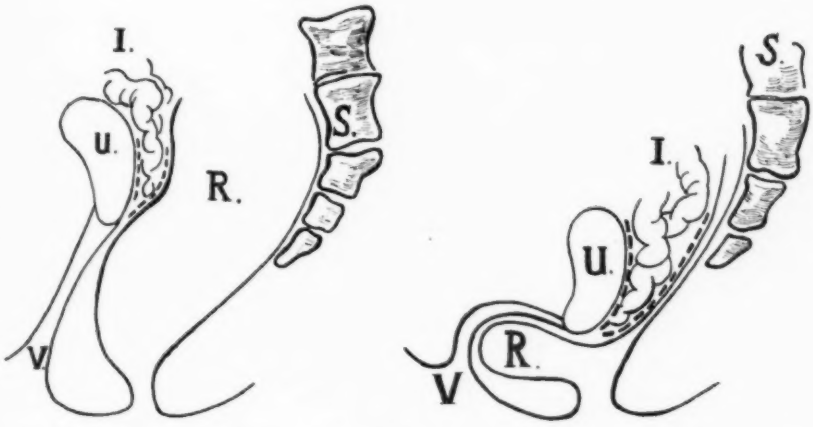


Fig. 3. Schematic representation of a uterus dropping backwards and downwards and a small proctocele forming during straining.

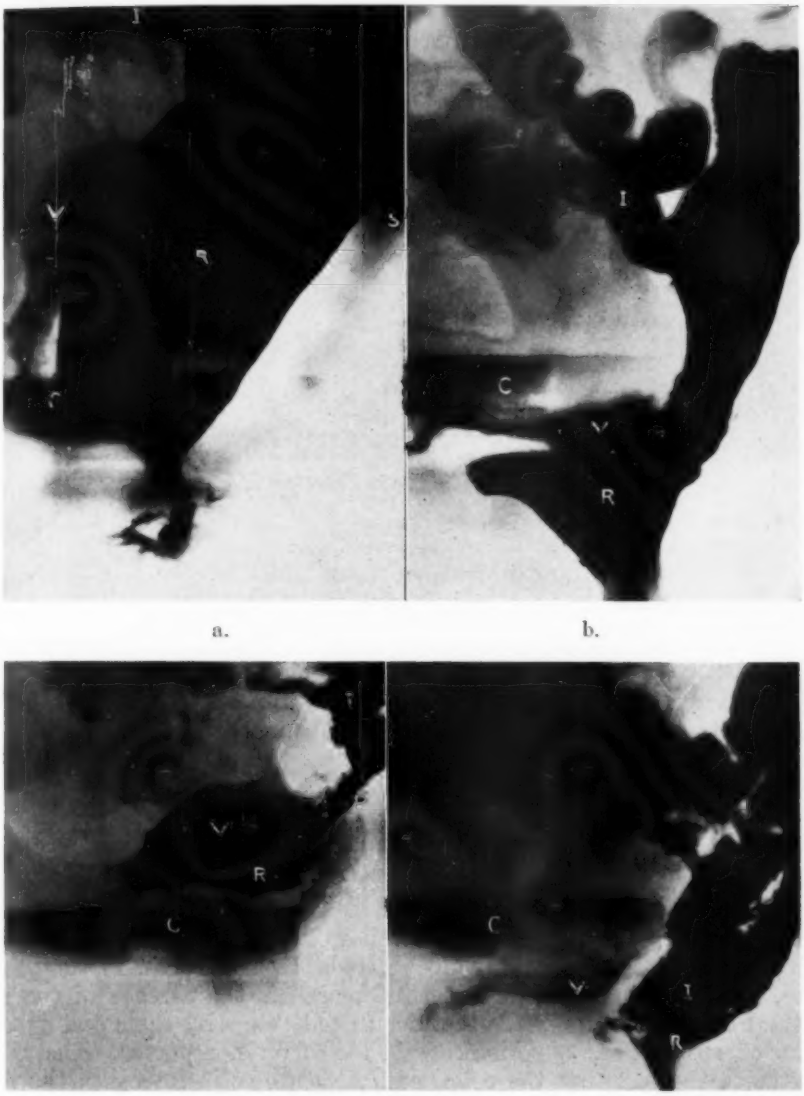
(figs. 3 (schema), 4 and 5). This change in position is often seen to best advantage in films taken after the evacuation of the contrast medium from the rectum. Among WALLDÉN's cases there were two of this type, although they are not discussed in any detail.

As a consequence of this sinking of the uterus the rectogenital fossa also becomes displaced, even reaching down to the anal canal in extreme cases, without having originally been abnormally deep. If intestinal loops sink down into the rectogenital fossa during straining, the blocking effect of the lowered uterus may be further exaggerated (cf. fig. 5 d).

Distention of the Lower Part of the Rectum

The rectum lies in a triangular space bounded laterally by the levatores ani, anteriorly by the septum rectogenitale and posteriorly by the sacrum, coccyx and ano-coccygeal raphe. The posterior wall remains practically stationary. The other walls are liable to give way, through congenital or acquired weakness, under the stress exerted during straining. Distention of the rectal wall then occurs either in a forward direction (proctocele, fig. 6) or laterally, the faeces being pressed down into the bulges thus formed (fig. 7). A symptom commonly complained of when such pockets are present is that the ampulla can only be emptied completely by pressure from without or sometimes by manual evacuation.

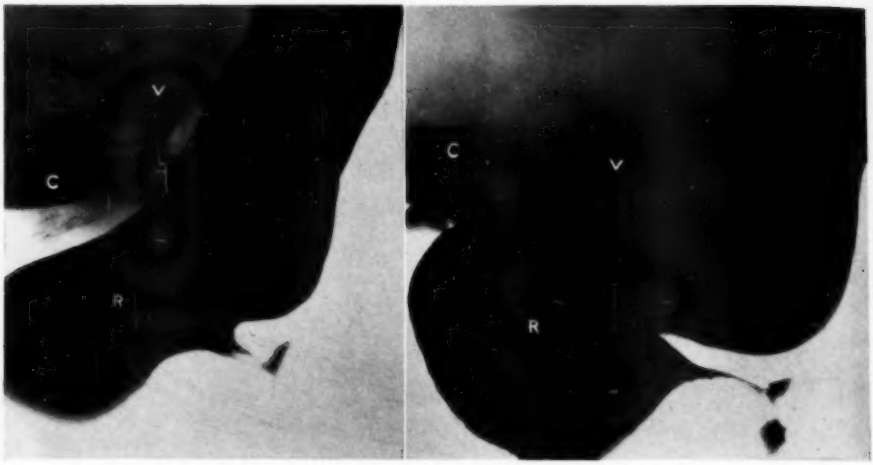
Fig. 4. A 46-year old woman with severe defaecation difficulties. a) and b) Lateral views with the patient at rest, and during straining. Most of the contrast medium has been evacuated. Obvious compression of the rectum during straining. The broken line shows the pelvic outlet.



a. b.

c. d.

Fig. 5. A 53-year old woman with typical symptoms. a) and b) Lateral views with the ampulla filled with contrast medium, with the patient at rest, and during straining. The uterus has produced a deep impression in the anterior rectal wall and during straining there is a small proctocele. c) and d) Lateral views after evacuation of the ampulla, at rest and during straining. An intestinal loop is pressed down behind the uterus in the direction of the inner orifice of the anal canal. The rectogenital fossa is of normal depth (palpated during an operation for gall-stones).



a. b.

Fig. 6. A 45-year old woman (Para II) with an enormous proctocele. a) Lateral view with the patient at rest. b) Lateral view during straining.

Pathophysiologic Principles in Mechanical Rectal Constipation

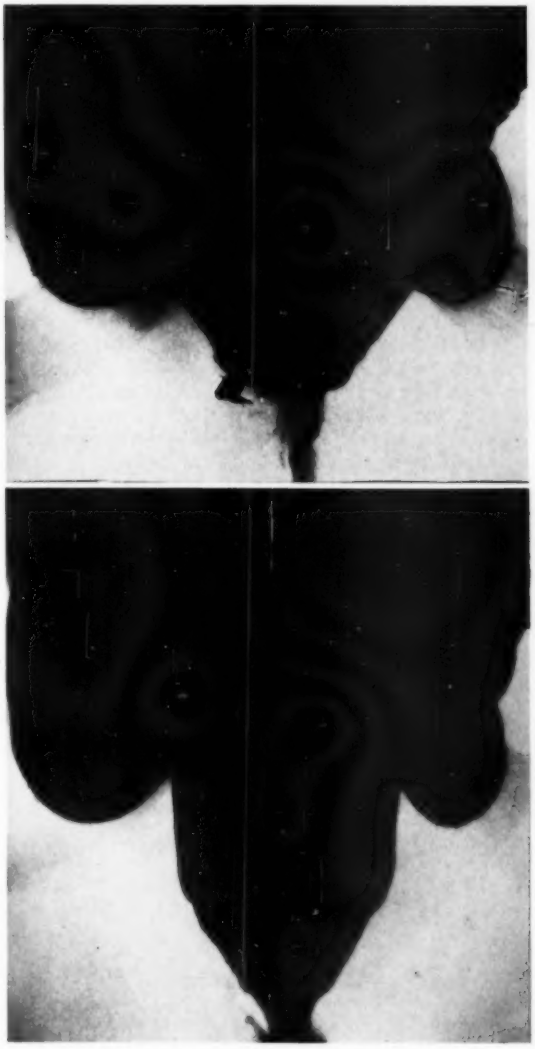
Defaecation is performed through a combination of two different functions:

1. Peristalsis in the distal colon and rectum.
2. Straining with the aid of abdominal muscles.

The rôle of these two functions varies in different individuals. When the colon peristalsis is weak, abdominal pressure plays the chief part in defaecation. If the septum rectogenitale, levators and uterus ligaments are stretched and slack there will arise defaecation difficulties of mechanical origin which can be particularly troublesome for those who rely chiefly on abdominal pressure when emptying the rectum. In the one type of rectal constipation, the bowel contents remain in pocket-like bulges and are not passed out through the anal canal. In the other type, the lowered uterus (or enterocele) hinders the passage of the intestinal contents through the rectum. In patients with signs and symptoms of obstruction, a periodicity factor is often reported. This may be due to the fact that the colon peristalsis varies in intensity, the patients' symptoms being aggravated in periods when the peristalsis is weak.

Treatment

Treatment varies according to the severity of symptoms. Evacuation difficulties may often be improved by medication. In more severe cases



a.

b.

Fig. 7. Pocket formations at the side of the rectum. a) and b) Antero-posterior views with the patient at rest, and during straining.

where operation is necessary, a radiographic examination will often indicate which operative method is likely to give the best results.

SUMMARY

About thirty patients with signs and symptoms of mechanical rectal constipation have been studied both clinically and radiographically by a special technique. Most of the patients were women. In the majority, it was found that in connection with straining at stool, the uterus dropped noticeably in a backward and downward direction, compressing the rectum and hindering defaecation. Intestinal loops, pressed down into a deep rectogenital fossa, also caused the same symptoms. Local distended areas, in which faecal contents had collected, were sometimes found in the distal part of the rectum.

ZUSAMMENFASSUNG

Ungefähr 30 Patienten mit Symptomen einer mechanischen Obstipation wurden sowohl klinisch als auch radiologisch mit einer speziellen Technik untersucht. Die meisten Patienten waren Frauen. In der Mehrzahl der Fälle fand man, dass der Uterus beim Stuhldrang deutlich nach hinten und unten sinkt und so das Rektum komprimiert und die Defäkation erschwert wurde. Darmschlingen, welche in eine tiefe Fossa rectogenitalis hineingepresst werden, verursachen ebenfalls die gleichen Symptome. Örtlich erweiterte Gebiete, in denen sich Fäkalien angesammelt hatten, wurden gelegentlich im distalen Abschnitt des Rektums vorgefunden.

RÉSUMÉ

Une trentaine de malades présentant des signes et symptômes de constipation rectale mécanique ont été étudies cliniquement et radiologiquement par une technique spéciale. La plupart de ces malades étaient des femmes. On a observé, le plus souvent, que, sous l'effet de l'effort de défécation, l'utérus descendait notablement en bas et en arrière, comprimant le rectum et faisant obstacle à la défécation.

Des anses intestinales, descendues dans un cul-de-sac recto-génital profond, causent aussi les mêmes symptômes. Daňs quelques cas on a trouvé des portions localement distendues de la partie distale du rectum où les matières fécales s'étaient accumulées.

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FROM THE ANATOMIC INSTITUTE, UNIVERSITY OF OSLO, NORWAY

GASTRIC CARCINOMA WITH SPECIAL REFERENCE TO THE SEX RATIO, AGE AND SITUATION AND TO THE ANATOMY OF THE STOMACH

by

Johan Torgersen

The sex ratio, the age curve and situation of gastric cancer are of importance in the study of the etiology of the disease. The literature shows that such data are difficult to obtain, due to the many pitfalls in the mortality and morbidity statistics. According to HANSEN (1950), about 30 per cent of the cases are not diagnosed, even in hospitals; latent tumours of the stomach are presumably relatively frequent in old people. In some countries too many cases may be recorded as cancer, in others too few.

The position regarding the site of the growth is no better, partly due to ignorance regarding the importance of precise localization, and partly due to a lack of knowledge of the anatomy of the stomach.

As far as cancer is concerned, the mucosa is of greater interest than the muscularis, which latter has generally formed the basis of the regional topography of the stomach. Not infrequently the muscular and mucosal topography is mixed; this is particularly the case regarding such ambiguous terms as 'pyloric part' and 'fundus'.

It is important that a study of the regional topography of the stomach includes a consideration both of the mucosa and the muscularis. As the radiologist locates a tumour from macroscopic observation, a consideration of the mucosa presumes a synthesis of the macroscopic and microscopic anatomy of the stomach. From a functional point of view the muscular and mucosal topography are integrated. The digestive part of the stomach containing the glandulae gastricae propriae, is remarkable for its weak musculature with a mainly retentive function. The chiefly

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motive part with its pyloric glands is characterised by a strong muscular coat, and has a retentive as well as a mixing and propelling function.

The border between the two types of glands is variable but generally lies above the angulus and about two inches from the pyloric sphincter on the greater curvature (see Diagram). The border on the greater curvature corresponds approximately to the upper boundary of the pyloric canal and on the lesser curvature to the upper boundary of the angular membrane; it is easily recognizable by the deep peristaltic waves which

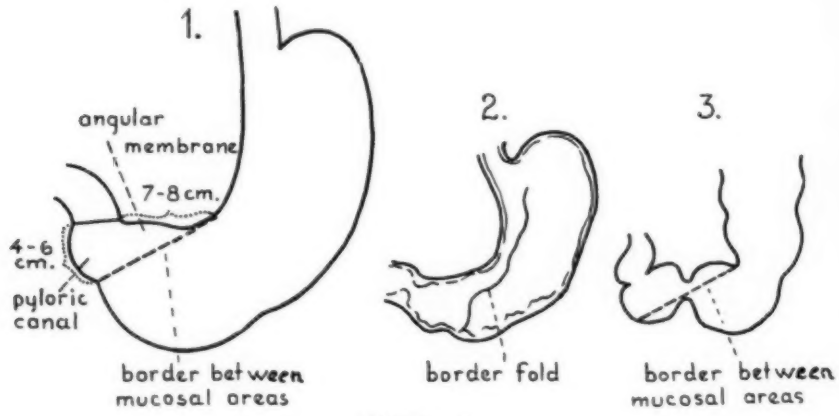

Diagram 1.

precede the waves of the pyloric canal. The transition between the mucosal areas or the mainly digestive and mainly motive parts is marked by the most prominent mucosal fold of the stomach, which runs from the isthmus and the end of the gastric canal towards the greater curvature somewhat above the border between the pyloric canal and the sinus.

These matters have been dealt with in some detail because the radiologist is in the best position to obtain data regarding the situation of a carcinoma both from the anatomic point of view and from the aspect of selection. A material comprising all first roentgen examinations in all out-patient departments in a certain geographic area forms a suitable one for statistical investigation.

Cancer of the stomach is generally considered as being a disease of the male, about two-thirds of the patients being of the male sex. The mortality statistics cannot be used to establish the absolute incidence of cancer in males and females. But as the errors of diagnosis and registration are probably the same in the sexes, they may be used to elucidate the sex ratio. HANSEN, who compared 639 autopsy cases with the clinical

records, came to the conclusion that the diagnostic errors showed the same frequency in males and females. One might expect some cases of gastric cancer in females, and particularly in young females, to be mistaken for ovarian cancers, a possibility which suggests a slight registration deficit in young females.

The age variations of the sex ratio in cancer of the digestive tract and the breast

	Oesoph.	Stomach	Colon	Rectum	Mamma
—40	1.36	1.01	1.12	0.57	0.006
40—49	2.46	1.41	0.77	1.26	0.006
50—59	2.46	1.62	0.91	1.60	0.005
70—	2.02	1.29	0.97	1.53	0.02

In the table the sex ratio in the years 1926—35 is calculated in different situations of cancer of the digestive tract and in the breast, the frequency in females being placed at 1.00. The frequencies in the sexes concern the relative incidences with consideration to the middle population size of men and women in the age groups compared in the same periods. In the group 'breast cancer in males' are included the data from 1942—45 in order to obtain a sufficiently large number. In all, twenty cases of breast cancer in males occurred in these fourteen years. The sex ratio in gastric cancer was calculated in the same way for the years 1936—40, 1942—45 and 1946—50. The ratios were approximately the same as in the years 1926—35. Below 40 years of age, the ratios were 1.09, 0.96 and 1.09 respectively. In all, one hundred and two cases of gastric cancer occurred below 30 years of age in the years examined, the sex ratio in this group being 0.80. The preponderance of males reaches a climax in the age group 50—69. After the age of 70 a levelling out of the sex difference takes place regarding all situations not excluding the breast.

Cancer of the large intestine which frequently occurs below the typical cancer age, is also relatively frequent in females, in contrast to cancer of the rectum which occurs particularly in males and in the ordinary cancer age. A calculation of the sex ratio in cancer of the small intestine, suggested that this situation is probably equally frequent in the sexes in all age groups.

In a previous study (TORGERSEN, 1944) it was shown that the site of election of cancer in the young was the region of the pyloric glands, whereas cancer in elderly people as well as in pernicious anaemia tended to be situated in the region of the gastric glands proper. These results have so far not been adequately checked. MOSBECH and VIDEBÆK (1950) in a study of carcinoma of the stomach in pernicious anaemia discussed vaguely defined terms, such as 'antrum' and 'fundus'. The data

obtained in the study in 1944 had the advantage that the situation was determined by the same standards in all groups. In 1948, GUISS and STEWART of the Memorial Hospital, N. Y., studied the site according to age in a surgical material. They could not confirm that cancer in the young prefers the pyloric part of the stomach. However, for obvious reasons such a material reveals more about the selection for surgery than about the situation of cancer in different age groups.

A greater curvature site is the most reliable indication that a tumour has originated in the region of the glandulae gastricae propriae. In the material of this study, 3.1 per cent of growths were found on the greater curvature in sixtyfour patients who were 40 years of age or younger, against 8.3 per cent in three hundred and eleven patients who were 41 years of age or older. Among one hundred and six cases of cancer in pernicious anaemia, twentyfive per cent were found on the greater curvature. Therefore it is probable that tumours in the region of the pyloric glands are relatively frequent in the young, whereas cancer in the older age groups and in pernicious anaemia selects the region of the glandulae gastricae propriae. Cancer in pernicious anaemia showed the same age distribution as cancer generally. Whether cancer of the stomach is relatively frequent in pernicious anaemia is hardly possible to decide at present. This is due to the chance of making the diagnosis of gastric carcinoma in patients with pernicious anaemia and others being possibly not the same. A higher incidence in pernicious anaemia may be due to fewer latent cases in these patients.

MCNEER (1941) made a study of cancer in the young; his paper was not generally accessible during the war. He came to conclusions which in many respects were in conformity with the results reported by the author in 1944. The two studies supplement each other; MCNEER did not consider the sex ratio in the population. In all, 682 cases belonging to all age groups from the Memorial Hospital were compared with about 500 cases of cancer in individuals below 31 years of age. Among these patients 46.7 were males, 48.1 were females, the sex not being recorded in the remainder of the cases. In the control group the ratio of males to females was 3 : 1. Gastric cancer in the young was thus found to be relatively frequent in females.

The situation was given in three hundred and forty-two cases, 64.9 per cent of growths being found at the pylorus against 34.9 per cent in the control group. Thus gastric cancer was found to select the pylorus in the young. Because cancer in the young selects both the pylorus and the female sex it is tempting to assume that the pyloric region is particularly predisposed to the development of cancer in young women. However, data regarding sex, age and situation are not available. In all 35.5 per cent of the young females showed metastases in the ovaries

against 4.4 per cent in the control cases. The corresponding numbers in peritoneal metastases were 22.9 per cent and 11.1 per cent, respectively.

It may be considered probable that the regions of the pyloric glands and of the gastric glands proper behave differently as far as the sex and age incidence of cancer is concerned. The region of the pyloric glands and the peritoneum apparently shares the susceptibility of the sex organs to cancer in young females. This observation, in connection with the relatively high incidence of cancer of the intestine, with the exception of the rectum, in young females suggests that the close developmental relationship between the intestinal entoderm, the peritoneal epithelium and the gonads manifests itself in a predisposition of these tissues to cancer in young females, both regarding primary tumours and metastases. The oestrogen sensitivity of the epithelium of the intestinal mucosa and the peritoneum has not been sufficiently examined so far. The particular predisposition of the region of the pyloric glands may be related to the demands on the hemopoietic function of the pyloric region in the fertile period in females, and may have a connection with the frequent occurrence of sideropenic anaemia in the same age group. A precancerous state on this basis in this part of the stomach may be supposed to be similar to the precancerous changes in the hypopharynx in sideropenic anaemia. It is remarkable that the roentgen appearances in gastritis of the pyloric canal and of the hypopharynx in sideropenia may show striking resemblances. The trend towards a proximal situation in elderly people may partly be due to a spread of the gastritis towards the cardia. However, the situation in pernicious anaemia suggests an influence of the hemopoietic function also in this case. The predisposition to gastric cancer in young females may partly be due to endocrine factors and partly to a greater heredity influence in young females in cancer of the stomach, as established for breast cancer by JACOBSEN (1947). The observations so far indicate that the distribution of gastric cancer between the two types of gastric mucosa is important to the etiology of the disease. Progress along this line depends on awareness of the problem on the part of radiologists.

SUMMARY

The sex ratio in gastric cancer is about 3 : 1 in the age group 40—70. Below 40 it is 1 : 1 and below 30, cancer of the stomach is probably more frequent in females than in males. Above 70, the frequencies in males and females tend to be levelled out. Cancer in the young is generally situated in the region of the pyloric glands, whereas in the ordinary cancer age the region of the gastric glands proper, is more often affected.

ZUSAMMENFASSUNG

Die Geschlechtsproportion beim Ventrikelkarzinom beträgt etwa 3 : 1 in der Altersgruppe zwischen 40 und 70 Jahren. Unter 40 Jahre ist das Verhältnis 1 : 1 und unter 30

Jahre ist der Magenkrebs wahrscheinlich bei Frauen häufiger als bei Männern. In der Altersgruppe über 70 Jahre neigt die Frequenz bei Männern und Frauen zur Angleichung. Bei jüngeren Individen hat der Krebs die Tendenz in der Gegend der Pylorusdrüsen aufzutreten, während das Magenkarzinom in üblichen mehr im Gebiet der eigentlichen Magendrüsen gelegen ist.

RÉSUMÉ

Le rapport des fréquences du cancer de l'estomac suivant le sexe est environ de 3 : 1 dans le groupe d'âge 40—70. Au dessous de 40 ans il est de 1 : 1 et au dessous de 30 le cancer de l'estomac est probablement plus fréquent chez les femmes que chez les hommes. Au dessus de 70 ans les fréquences chez les hommes et chez les femmes tendent à s'égaler. Chez les jeunes, le cancer siège plutôt dans la région des glandes pyloriques, alors qu'à l'âge habituel du cancer il tend plutôt à siéger dans la région des glandes proprement gastriques.

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EXPERIENCE WITH THE 30 MeV SYNCHROTRON AS A RADIOTHERAPEUTIC INSTRUMENT

II. Dosimetry and relevant physical measurements

by

J. S. Mitchell, C. L. Smith, D. J. Allen-Williams and *R. Braams*

The fundamental problems of the dosimetry of 30 MeV_p roentgen radiation are as yet incompletely solved. (See for example, FANO and TAYLOR, 1950, MAYNEORD and MARTIN, 1950, FAILLA 1951, QUIMBY 1951, I. C. R. U. 1951.)

As a basis for the approximate measurements necessary for practical radiotherapy, it is considered that for this radiation, the definition of the roentgen unit can be fulfilled with sufficient accuracy to enable intercomparison of the dose rate in the primary beam for different machines.

In considering the validity and application of the Bragg-Gray conditions in cavity ionisation chamber measurements with 30 MeV_p roentgen rays, it is found experimentally that electronic equilibrium is established in a wall of approximately air-like solid medium of thickness 5.0—5.5 g per cm^2 surrounding a small air filled ionisation chamber. The absorption of annihilation radiation of energy 0.51 MeV and of the radiation losses from the faster secondary electrons appear to be taken into account as a first approximation. It will be shown that fast neutrons in the primary beam, thermal neutrons and the radio-activity induced in the medium of the wall make negligible contributions to both the physical dose and the biological effects.

At these high energies, it is difficult to specify the exact point in the roentgen ray beam to which the ionisation measurement made in e. s. u. per cc of standard dry air refers. However, for the purpose of

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intercomparison of machines, this fundamental difficulty can be avoided by the use of defined experimental conditions. With the filtered 30 MeV_p roentgen radiation, there appears to be no difficulty in fulfilling the condition that the linear dimensions of the air cavity in the ionisation chamber are small with respect to the range of the secondary electrons in air. The definition of the experimental conditions required for intercomparison does not appear to be critical. The experimental arrangements which we have used are intended to enable comparison with those of other workers (see MAYNEORD and MARTIN 1950).

From the point of view of the treatment, the ultimate requirement of dosimetry is a measure of the energy absorption per unit mass, *e. g.* ergs per g, of tissue at each point. Calorimetric dosimetry is still extremely difficult but has been applied to this problem (LAUGHLIN 1952). It should be possible in the not too distant future to correlate the dose in ergs per g of tissue with the roentgen unit on the basis of direct measurements. At present one must rely on ionisation measurements made with a thin walled ionisation chamber in a suitable phantom. For measurements near the front surface of the phantom — which it is emphasized are not in r — an extrapolation chamber has been used.

Practical Dosimetry

As a provisional basis for dosimetry, one must refer to an experimental sub-standard which is easily reproducible and carefully defined. We have used a 100 r Victoreen chamber placed with its axis transversely to the axis of the roentgen ray beam at the centre of a "cubical" block of Perspex of measured density 1.19[1] g per cm^3 and with edges of lengths 10.0, 10.0 and 10.5 cm, the last dimension being parallel to the long axis of the Victoreen chamber. The volume of the chamber determined radiographically (by Miss R. SAUNDERS) was 0.405 cm^3. The unit based on this experimental arrangement is called "r" in this paper.

The isodose curves were measured with a "small thin-walled" Perspex ionisation chamber of which details are given by ALLEN-WILLIAMS (1952 p. 99) and in which the diameter was 9 mm and the effective collecting volume is 0.572 cc. Readings were taken of the ionisation chamber current at a number of points in a 30 cm cubic water phantom. Following all workers since QUASTLER et al. (1949), the maximum value of the readings was taken as 100 %. In practice the readings were plotted from front to back, along the axis of the beam; then the remote control apparatus was turned through a right angle and readings taken across the beam at different distances from the front of the tank. A very large number of measurements have been made under different conditions.

Measurements near the surface have been made by means of extrapolation chambers with front walls of polythene films and of aluminium.

The extrapolated surface ionisation per unit volume was found in this way to be 12 % of the maximum under the present experimental conditions.

Ultra-Fractionation of Roentgen Rays from the Synchrotron

The roentgen radiation from the synchrotron is pulsed in a characteristic manner (Figure 1) which must be taken into account in considering the accuracy of ionisation measurements and the problem of the relative biological efficiency. The roentgen radiation is produced in main pulses at the rate of 50 per second. Each main pulse is of duration about 100 microseconds and consists of about 50,000 short pulses each of duration about 1×10^{-9} second due to "bunching" of the circulating electrons. (In machines with pulsed extractor circuits, the main pulses are of length about 1 microsecond.)

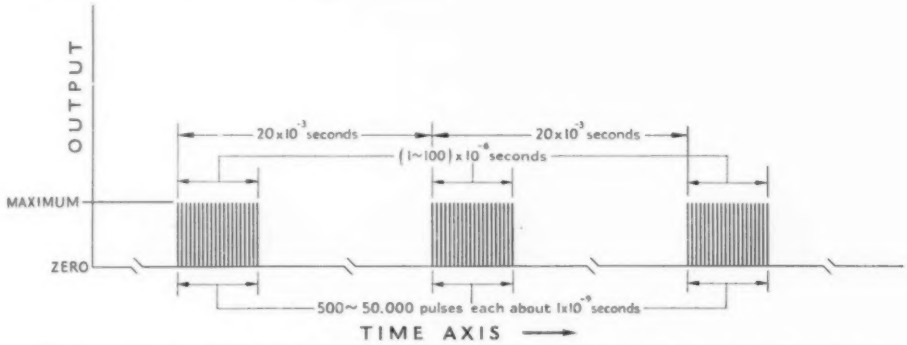

Fig. 1. Diagram of the "ultra-fractionation" of the roentgen radiation produced by the synchrotron.

The problem of ionisation measurements in pulsed radiation beams has been studied by Boag (1950, 1952). Using Boag's theory to calculate the collection efficiency, it was found that for the 100 r Victoreen chamber, and our probe and monitor chambers, the ionisation current readings are respectively 100, 99 and 98 per cent of the theoretical maximum values. This conclusion is supported by measurements of the saturation curves using radium sources and the synchrotron, although it was difficult to keep the output of the synchrotron constant to within ± 1 per cent.

Depth Dose Distribution and Isodose Curves

In Table I are given the values which are considered to be the most reliable obtained for the depth doses measured in the water phantom

Table I

Axial depth doses measured in water phantom for roentgen radiation from synchrotron for different sizes of circular fields.

F.S.D. 100 cm. The value at the maximum is taken as 100.

Field size: Nominal diameter	7.5 cm	5 cm			2 cm
Maximum energy, MeV	30.0 ± 0.4	33.0 ± 0.4	30.0 ± 0.4	27.0 ± 0.5	30.0 ± 0.4
Depth					
0 mm.	~ 12	~ 12	~ 12	~ 12	~ 12
5 mm.	60.0	58.5	60.0	63.0	60.0
1 cm.	72.5	69.5	73.5	76.0	75.0
2 cm.	88.0	85.0	89.0	91.0	91.0
3 cm.	96.0	95.0	96.5	97.5	98.0
4 cm.	100.0	100.0	100.0	100.0	100.0
5 cm.	100.0	100.0	100.0	100.0	100.0
6 cm.	100.0	100.0	99.5	98.0	99.0
7 cm.	98.5	99.0	97.5	95.0	96.0
8 cm.	95.5	96.5	94.5	91.0	91.5
9 cm.	92.0	93.0	91.0	87.5	87.5
10 cm.	88.0	89.0	87.0	84.0	84.0
11 cm.	85.0	85.5	83.5	80.5	80.5
12 cm.	81.5	82.0	80.5	77.5	77.0
13 cm.	78.5	79.0	77.0	74.0	74.0
14 cm.	75.5	76.0	74.0	71.5	71.0
15 cm.	72.5	73.0	71.0	68.5	68.0
16 cm.	69.5	70.0	68.0	66.0	65.0
17 cm.	67.0	67.5	65.5	63.0	62.5
18 cm.	64.0	65.0	63.0	60.5	59.5
19 cm.	62.0	62.5	60.5	58.0	57.0
20 cm.	59.5	60.0	58.0	55.5	55.0
21 cm.	57.0	57.5	55.7	53.5	52.5
22 cm.	55.0	55.5	53.5	51.3	50.5
23 cm.	52.5	53.3	51.5	49.0	48.5
24 cm.	50.5	51.0	49.5	47.3	46.5
25 cm.	48.8	49.3	47.5	45.5	44.5
26 cm.	46.8	47.5	45.5	43.5	42.5
27 cm.	45.0	45.5	43.8	41.8	41.0
28 cm.	43.0	43.8	42.0	40.0	39.0
29 cm.	41.5	42.0	40.3	38.5	37.5
30 cm.	40.0	40.5	38.5	37.0	36.0

The experimental error is estimated at ± 3 % for depth 5 mm, ± 2.5 % for depths 1 and 2 cm, and ± 1.5 % for greater depths.

on the axis of the filtered roentgen ray beam from the synchrotron for circular fields of nominal diameter 7.5, 5, and 2 cm. In each case, the value at the maximum is taken as 100 and the F. S. D., meaning the

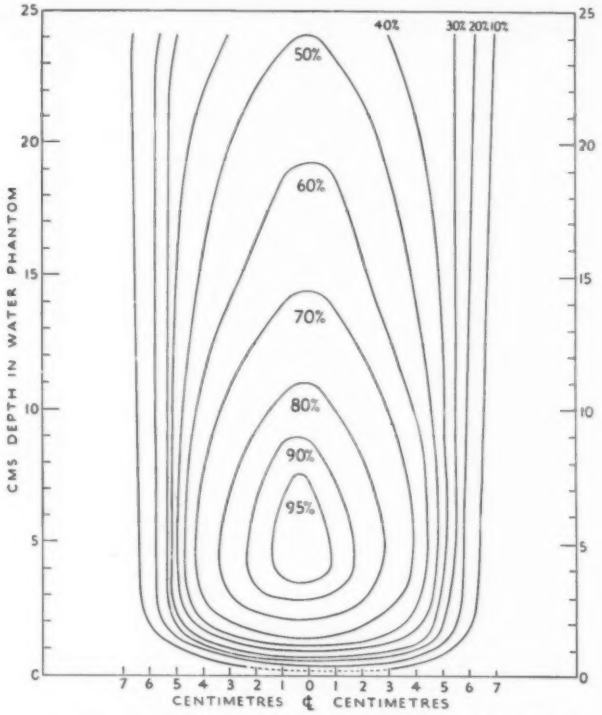

Fig. 2. Depth dose distribution in the water phantom for the *unfiltered* roentgen ray beam from the synchrotron.
"9 cm diameter" circular field.
Peak energy 30.0 ± 0.4 MeV. F. S. D. 100 centimetres.

distance from the target to the entrance surface of the anterior wall of the phantom, is 100 cm. The values refer to maximum energy 30.0 ± ± 0.4 MeV with additional values for 27.0 ± 0.5 MeV and 33.0 ± 0.4 MeV in the case of the 5 cm diameter field. The experimental error is estimated at ± 3 %, for depth 5 mm, ± 2.5 % for depths 1 and 2 cm and ± 1.5 % for greater depths.

It will be seen that the depth dose values show a small variation with field size. For depths greater than that of the maximum there is a small increase in depth dose with increasing field size, similar to that found by LAUGHLIN, BEATTIE, LINDSAY and HARVEY (1951) for 25 MeV roentgen rays.

When the maximum energy is increased from 27 to 33 MeV, the depth of the maximum increases by about 0.8 cm, and the depth dose

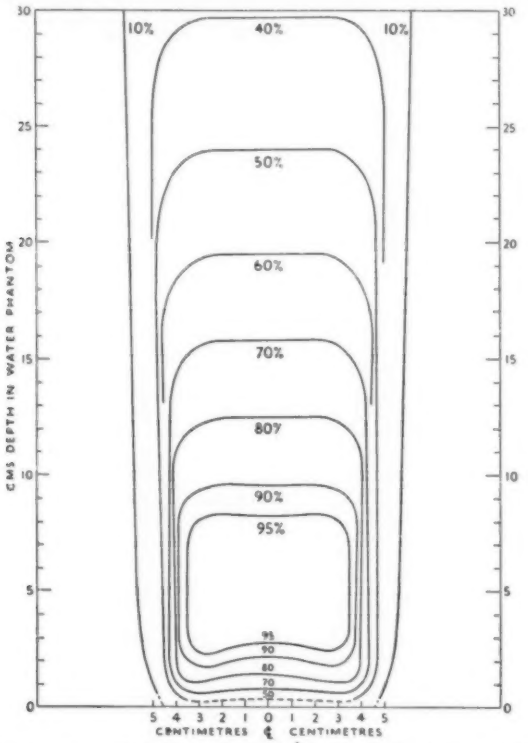

Fig. 3. Depth dose distribution in the water phantom for the *filtered* roentgen ray beam from the synchrotron.
"7.5 cm diameter" circular field.
Peak energy 30.0 ± 0.4 MeV. F. S. D. 100 centimetres.
"Conical" copper filter *in situ*.

values correspondingly decrease slightly for depths less than that of the maximum and increase slightly for depths greater than that of the maximum.

Although the depth dose values are less reliable for points near the field edges, it is necessary to consider the isodose curves. The dose distribution in the water phantom for the unfiltered beam is shown in Figure 2 and is similar to the curves published by ADAMS et al. (1948) and CHARLTON and BREED (1948). It is generally agreed that this type of isodose curve is unsuitable for radiotherapy and much more convenient distributions have been obtained with the aid of compensating filters (ADAMS et al. 1948, QUASTLER et al. 1949, JOHNS et al. 1949,

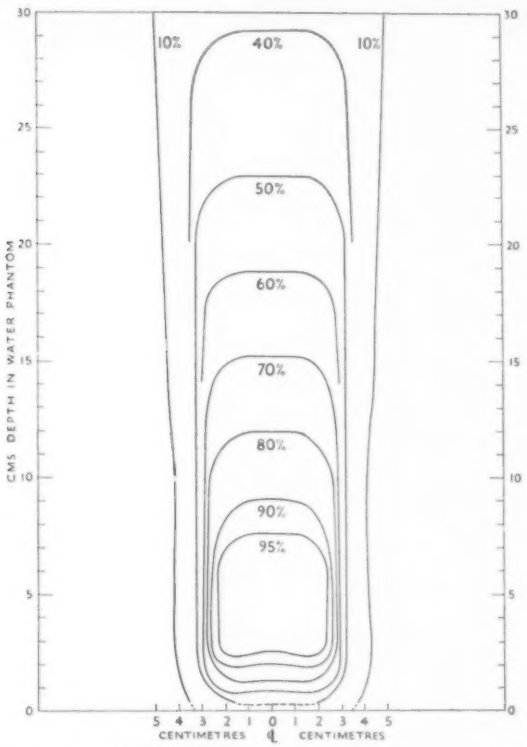

Fig. 4. Depth dose distribution in the water phantom for the *filtered* roentgen ray beam from the synchrotron.
"5 cm diameter" circular field.
Peak energy 30.0 ± 0.4 MeV.
F. S. D. 100 centimetres. "Conical" copper filter *in situ*.

1952, LAUGHLIN et al. 1951). It is emphasized that the detailed distribution depends upon the geometry of the compensating filter.

The best values for the isodose curves obtained with the filtered roentgen ray beam from the Cambridge 30 MeV synchrotron are given in Figures 3, 4, 5. These results refer to maximum energy 30.0 ± 0.4 MeV with the copper conical filter of section and dimensions given in Part I Figure 5. The F. S. D. is 100 cm. The isodose curves in which we have been most interested are for the "7.5 cm diameter" circular field (Figure 3), the "5 cm diameter" field (Figure 4) the "2 cm diameter" field (Figure 5), and the "5 cm diameter" field at 45° incidence (Figure 6). Measurements have also been made of the effects

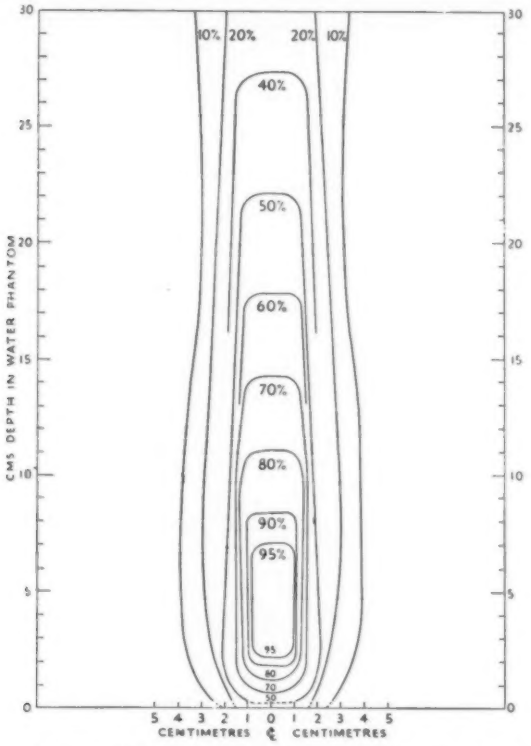

Fig. 5. Depth dose distribution in the water phantom for the *filtered* roentgen ray beam from the synchrotron.
"2 cm diameter" circular field.
Peak energy 30.0 ± 0.4 MeV.
F. S. D. 100 centimetres. "Conical" copper filter *in situ*.

of partial shielding of the field by a lead brick "eyeshield" of thickness 2 inches and of a centrally placed lead stop.

The "7.5 cm diameter" circular field (Figure 3) is perhaps the most useful. The 100 % region lies at about 5 cm depth, and the plane circular part of the 50 % surface lies at depth 24 cm. The 90 % isodose surface is approximately a cylinder of diameter 7.6 cm and length 7.5 cm extending along the axis of the beam from depth 2.0 to 9.5 cm.

The 90 % isodose cylinder is of diameter 5.2 cm for the "5 cm diameter" field and diameter 2.0 cm for the "2 cm diameter" field.

It will be seen that these isodose curves show no evidence for the steep dosage gradients and discontinuities found at the geometrical edge

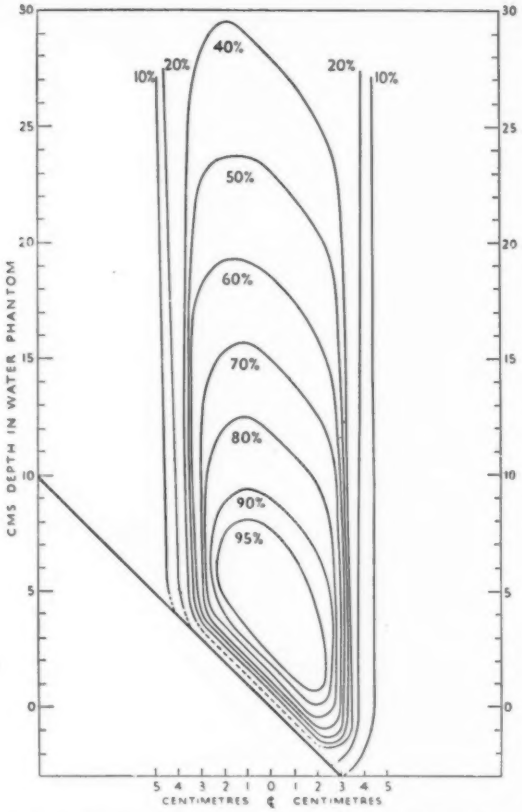

Fig. 6. Depth dose distribution in the water phantom for the *filtered* roentgen ray beam from the synchrotron.
"5 cm diameter" circular field at 45° incidence.
Peak energy 30.0 ± 0.4 MeV.
F. S. D. 100 cm. "Conical" copper filter *in situ*.

of the beam by LAUGHLIN et al. (1951). This is almost certainly due to the relatively large diameter, 9 mm, of the ionisation chamber used. Attempts to correct the measurements for the finite size of the ionisation chamber by means of theory developed by two of us (C. L. S. and R. B.) did not appreciably sharpen the edge of the beam. Further measurements are necessary. However, the method of measurement used proved fairly sensitive in detecting slight irregularities in the beam edge which were confirmed radiographically.

Oblique incidence of the fields has been studied by QUASTLER et al. (1949), JOHNS, DARBY and KORNELSEN (1951) and LAUGHLIN et al. (1951). Our measurements at 30 MeV for the "5 cm diameter" circular field at 45° incidence (Figure 6) show only a slight "refraction" with an angle of about 8° between the surface and the tangents to the isodose curves at the axis of the beam.

With the present design of magnet, the shortest F. S. D. obtainable for practical treatment is 85 cm.

Relevant Physical Experiments

Many physical measurements have been made. Of radiological interest are measurements by means of ionisation chambers of back-scatter and of absorption coefficients, and studies of photo-nuclear reactions and induced radio-activity in tissues (BRAAMS 1952).

Back-Scatter

In general back-scatter is small but not negligible. It is roughly proportional to the atomic number of the material, and includes soft radiations in addition to the hard components. The backscatter from bone will increase the dose in the immediately adjacent tissue by about 10 %.

Absorption

For measurement of the absorption coefficients of different materials, the narrow collimated roentgen ray beam was circular in cross section of diameter 1 cm at 100 cm from the target, and passed through the centre of the ionisation chamber, the sensitive area of which was at least 2.1 × 2.1 cm. The distance from the absorber to the ionisation chamber was 30 cm so that secondary roentgen radiation produced in the absorber made negligible contribution to the ionisation current. A block of copper 8 mm thick was placed immediately in front of the ionisation chamber to remove secondary electrons produced in the absorber and in the intervening air, and also to increase the ionisation current.

Some of the results of these measurements are given in Table II. It is of particular interest that for the filtered beam, the mass absorption coefficient has the same value, within the accuracy of the measurements, for water and bone. Taking into account the density of bone, this result makes it possible to correct the depth dose distribution for transmission through intervening bones as in the treatment of intracranial tumours.

Table II

Measurements of absorption coefficients for 30 MeV$_p$ roentgen radiation from the synchrotron with and without the copper compensating filter

Material	Density	Mass absorption coefficient, cm²/g	
		Without filter	With filter
Water	1.00	0.0260	0.0248
Phantom wax (a)	0.99	0.0261	0.0252
Distrene (b)	1.06	0.0252	0.0218
Perspex (c)	1.19[1]	0.0254	0.0228
Bone (d)	1.96	0.0265	0.0246
Lead	11.37	0.0551	0.0544

(a) Mixture of paraffin wax (60.8 %), polyethylene (30.4 %), magnesium oxide (6.4 %) and titanium oxide (2.4 %), (JONES and RAINE 1949).
(b) Polymer of C_8H_8.
(c) Polymer of composition $(C_5H_8O_2)_n$, similar to lucite.
(d) Plates of horse bone saturated with water.

There is insufficient evidence to determine exactly the dose received by the living cells in the Haversian canals and lacunae in irradiated bones at various depths in the body. However, as a first approximation it can be obtained from a depth dose curve by multiplying the dose in water at the same depth in g per cm² by the density of the bone.

Photonuclear Reactions and Induced Radioactivity

It is calculated that for the 30 MeV$_p$ roentgen rays from the synchrotron the contributions to the dose in muscle in energy absorption per g are respectively 0.02 % from induced radio-activity, 0.07 % from photo-neutrons produced in (γ, n) reactions and 0.2 % from photo-protons produced in (γ—p) reactions. The photo-nuclear contributions are mainly from oxygen atoms and to a less extent from carbon and nitrogen atoms. It may be assumed that the relative biological efficiency per ion pair for the photo-protons and the recoil protons produced by photo-neutrons, in relation to the high energy roentgen rays has a value in the region of 5 to 10. Accordingly it is reasonable to conclude that the photo-protons and photo-neutrons contribute less than 3 % to the biological effects produced in muscle by the 30 MeV$_p$ roentgen rays.

These calculations confirm the results of the earlier ones (MITCHELL 1946 a and b) and the experiments and calculations of MAYNEORD, MARTIN & LAYNE (1949) and JOYET (1952). However, it now appears that photo-protons play the largest part in the small contribution made by photonuclear processes and induced radio-activity to the biological effects produced in soft tissues by 30 MeV$_p$ roentgen rays. Under these

conditions the induced radio-activity *per se* appears to have negligible effects.

In making similar calculations for bone, it was necessary to obtain further evidence concerning the energy of the positrons emitted by Ca^{39} of half-life 1.06 ± 0.03 seconds (HUBER, LEINHARD, SCHERRER and WÄFFLER 1943) and the neutron yield in the reaction Ca^{40} (γ, n) Ca^{39} (BRAAMS 1952).

A sample of calcium metal 3.5 mm thick and coated with a thin layer of paraffin to reduce oxidation was irradiated by the synchrotron for 3 seconds and then by a mechanical device allowed to fall in front of a G. M. 4 Geiger counter for 12 seconds. The scaling unit and counter were switched off during the irradiation. The pulses were also photographed on a double beam cathode ray oscillograph with a 50 cycle per sec. sinusoidal wave for timing. Clean non-radio-active air was blown on to the sample and counter, which were adequately shielded with lead. Absorption measurements of the positrons were made in aluminium by the method of FEATHER (1938). The range was found to be 3.48 g per cm^2. Some experiments were also made of the absorption in lead to exclude the presence of γ-rays. From the range-energy relation determined by FEATHER, the energy of the positrons from Ca^{39} was found to be 6.7 ± 0.5 MeV.

The induced activities of copper and calcium were compared. The approximate value of the neutron yield in the γ, n reaction in Ca^{40} was 4,700 n per g per r.

Calculations have been made of the contributions of photonuclear reactions and induced radio-activity to the energy absorption in 1 g of bone when the surrounding soft tissue is irradiated with 1 r of the roentgen radiation from the synchrotron of maximum energy 27 MeV. The contributions to the energy absorption are respectively 0.18 % from photo-protons, 0.07 % from photoneutrons and about 0.025 % from induced radio-activity. Hence again for bone, it is reasonable to conclude that photo-protons and photoneutrons contribute less than 3 % to the biological effects of the 30 MeV_p roentgen rays, while the induced radio-activity *per se* appears to make a negligible contribution.

Fast Neutrons in the Beam

Some preliminary measurements of the fast neutron flux from the 14 MeV synchrotron at Malvern were made by ALLEN-WILLIAMS and APPLEYARD (1949). LAUGHLIN (1951) in discussing the use of a 23 MeV betatron for radiotherapy concludes that the biologically effective dose contributed by external neutrons is slightly more important than that of stray roentgen radiation but that all these contributions are suf-

ficiently small to be well below the maximum permissible dose. Our own calculations and measurements support this conclusion.

With our synchrotron the most important sources of fast neutrons are the copper compensating filter and the lead of the collimators. The thresholds for the γ, n reactions in copper and lead are respectively 10.9 and 7.9 MeV. Probably the average energy of the fast neutrons concerned is in the region of 10 MeV. Measurements were made at many points in the water phantom of the induced activity in indium foils, with and without cadmium shielding. The maximum indium activity was found in the centre of the beam at a depth of about 5 cm. The form of the curves suggests that most of the slow neutrons (thermal neutrons and 1.44 e. v. indium resonance neutrons) result from slowing down of fast neutrons produced externally. We also tried to make measurements by the permanganate method (ERBER et al. 1950) but without success almost certainly because the neutron flux was too low.

Calculation shows that the fast neutron flux due to photo-neutrons produced by the 30 MeVp roentgen radiation in the copper cone has the value at 100 cm from the target of 31 n per cm² per sec. for a dose rate of 10 "r" per minute. This value is based on the value of 5.75×10^4 n produced per g of copper per "r", with the assumptions that the photo-neutrons are emitted with spherical symmetry and none are absorbed in the copper cone. The neutron flux may be increased by a factor of 2—3 by canalisation. Hence during treatment the value of the fast neutron flux in the beam at the position of the patient is of the order of twice a reasonable value (3—40 n per cm² per sec.) for the maximum permissible flux of 10 MeV neutrons for continuous exposure for 8 hours (see MITCHELL 1947 b, 1952, EVANS 1949, TAIT 1950).

Measurements have been made of the thermal neutron flux during treatment at different positions on and near the patient. Indium foils were used. The values of the thermal neutron flux per tumour "r" at F. S. D. 100 cm were $1—3 \times 10^4$ n per cm² and less. These values are again of the same order as the maximum permissible flux of thermal neutrons for continuous exposure for 8 hours (MITCHELL 1947 a, 1952, SNYDER 1950).

Accordingly, it can be concluded that the biological effects of fast neutrons in the beam are negligible.

Measurement of Stray Radiation.

(a) *Protection of the patient.*

Measurements of the intensity of roentgen radiation at points on the patient outside the beam were made by means of dental films and small ionisation chambers. With a 2 inch thick lead brick shield, the

dose received by the patient outside the beam lies between about 1/2 and 1 r per 1,000 "r" delivered to the tumour.

(b) *Protection of the staff.*

Many measurements have been made of the intensity of stray radiation in the building housing the synchrotron. The synchrotron room is 28 ft. long in the direction of the beam, by 21 ft. wide, with a simple maze entry; its walls are of concrete in brick, of thickness in the direction of the beam 6 ft. and elsewhere 4 ft. The position of the operator at the controls outside is at slightly more than a right angle to the direction of the beam with two intervening 4 ft. thicknesses of wall. For an output of 10 "r" per minute in the filtered beam at F. S. D. 100 cm, the dose rate at the position of the operator is not more than 10 mr per 8 hours. The operator views the patient through the $4\frac{1}{2}$ ft. water window by means of a mirror, to avoid any possibility of leakage of radiation around the edges of the water window. Similar low values of the radiation intensity are found in the adjacent rooms except at the entry to the synchrotron room and in the condenser room in the line of the beam where the intensity is about 40 mr per 8 hours, and also along a narrow region at about 45° to the beam where after oblique passage through about 5 ft. of concrete and brick the intensity is about 25 mr per 8 hours. This very weak "beam" appears to be due to radiation coming from the resonator and escaping between two of the return paths of the magnet. Within the synchrotron room, the intensity of radiation is very much higher except in the shadow of the lead screen to protect the patient. For example, at positions at the sides of the synchrotron behind the screen, the intensity may reach 15 r per 8 hours. However, no one works in the synchrotron room when the machine is running. Outside the synchrotron building, the radiation is negligible.

Discussion

The measurements described appear to provide a practical basis for dosimetry in 30 MeV_p roentgen ray therapy. At the present stage, the measurements of dose rate for the primary beam refer to an experimental substandard which is carefully defined. The unit based on this experimental arrangement is called "r" but great caution is necessary in attempting to relate this unit to the roentgen unit. It seems reasonable to measure the dose in "r" for depths in the phantom greater than the equilibrium thickness. For measurements near the front surface of the phantom, an extrapolation chamber has been used but it is emphasized that the measurements are not in "r". Fortunately the exact values of the dose near the surface are not of great clinical importance.

The ultra-fractionation of the roentgen radiation from the synchrotron appears to present no serious difficulty from the point of view of physical dosimetry. However, it is essential to consider it in quantitative studies of the biological effects.

The depth dose distributions are of particular interest. The values given in Table I for the depth doses on the axis of the filtered beam are based upon those measurements which we have considered to be the most reliable. The values near the field edges are appreciably less reliable, and are subject to experimental error on account of the relatively large diameter, 9 mm, of the ionisation chamber used. Nevertheless, the approximate isodose curves are essential for practical radiotherapy.

Among the physical measurements of radiological interest it is important to mention that for the filtered 30 MeV_p roentgen radiation, the mass absorption coefficient has the same value, within the accuracy of the measurements for water and bone. This result makes it possible to correct the depth dose distributions for transmission through intervening bones and also shows that there is no serious preferential energy absorption in the living cells in irradiated bones attributable to pair production.

It can be concluded that photonuclear reactions and induced radioactivity make no appreciable contributions to the biological effects of 30 MeV_p roentgen radiation for both soft tissues and bone. Further, the biological effects of the fast neutrons in the beam, which probably are produced mainly in the copper compensating cone, appear to be negligible.

With regard to protection of the patient, it is considered essential to employ lead shielding so that the dose received by the patient outside the beam does not exceed $^1/_2$—1 r per 1,000 "r" delivered to the tumour.

With the present arrangements for housing and working the synchrotron, the dose of radiation received by the staff does not exceed 10 milliroentgens per 8 hours irradiation. This value confirms the substantial margin of safety provided by the protection arrangements.

SUMMARY

The paper summarizes measurements carried out to provide a practical basis for dosimetry in 30 MeV_p roentgen therapy. The ultra-fractionation of the radiation appears to present no serious difficulty in dosimetry but must be taken into account in quantitative studies of the biological effects.

Information of radiological interest is given concerning measurements of back scatter, absorption coefficients and stray radiation. Studies of photonuclear reactions, induced radioactivity, and fast neutrons in the beam confirm that these factors are not likely to be of importance in 30 MeV_p roentgen therapy.

ZUSAMMENFASSUNG

Im Aufsatz werden Messungen beschrieben, die ausgeführt wurden, um eine praktische Grundlage für die Dosimetrie bei der 30 MeV Röntgentherapie zu erhalten. Die Ultrafraktionerung der Strahlung scheint für die Dosimetrie keine ernstlichen Schwierigkeiten zu bieten; sie muss jedoch bei quantitativen Studien über die biologischen Wirkungen berücksichtigt werden.

Informationen von radiologischem Interesse bezüglich Messungen des «back-scatters», der Absorptionskoeffizienten und der Streustrahlung werden mitgeteilt. Studien über die photo-nukleären Reaktionen, die induzierte Radioaktivität und die schnellen Elektronen im Strahl bestätigen, dass diese Faktoren bei der 30 MeV Strahlentherapie wahrscheinlich keine Rolle spielen.

RÉSUMÉ

Cet article résume les mesures faites en vue de fournir une base pratique à la dosimétrie en roentgenthérapie à 30 $MeV_{max.}$ L'ultra-fractionnement du rayonnement ne semble pas présenter de sérieuse difficulté en dosimétrie, mais on doit en tenir compte dans les études quantitatives des effets biologiques.

Des notions intéressantes du point de vue radiologique sont données sur les mesures du rayonnement secondaire, des coefficients d'absorption et du rayonnement diffusé. L'étude des réactions photonucléaires, de la radio-activité induite et des neutrons rapides dans le rayonnement confirme que ces facteurs ne sont vraisemblablement pas importants en radiothérapie à 30 $MeV_{max.}$

REFERENCES

See Part I, Acta radiol. 40 (1953), 419.

FROM KING GUSTAF V JUBILEE CLINIC (DIRECTOR: B. EBENIUS), LUND, SWEDEN

THE FREQUENCY OF OVARIAN TUMOURS AND OF ESTRUS IN MICE TREATED WITH ROENTGEN RADIATION AND HORMONES

by

Stig Kullander

In an investigation of the effect of roentgen rays on the frequency of tumours in mice, FURTH & FURTH (1936) observed, among other things, that such radiation increases the frequency of ovarian and pulmonary tumours but decreases that of mammary carcinoma. The mice were 5—10 weeks old at the time of irradiation. The entire body was irradiated. Each mouse received altogether 200—400 r, given as a single dose or as fractional doses. The relative increase in the incidence of ovarian tumours was practically one and the same in all three stocks used, but the absolute frequency varied considerably. Most of the ovarian tumours appeared at 16 months, the earliest at 5 months.

FURTH & BUTTERWORTH (1936) and BUTTERWORTH (1937) made a more detailed study of such ovarian tumours in irradiated mice. They distinguished three types: a) *granulosa cell tumours* built up of cells apparently morphologically related to those of the ovarian follicles, b) *luteomas*, a variant of granulosa cell tumours, with large pale-staining cells containing much fat in the cytoplasm and c) *tubular adenomas*. Granulosa cell tumours and luteomas are usually seen as mixed tumours, are hormone producing, and vaginal smears from animals with such lesions show the cytologic picture seen in estrus. Tubular adenomas do not seem to produce hormones. They probably arise as a result of proliferation and ingrowth from the lining epithelium of the ovary, while the hormone-producing tumours develop from interfollicular parenchyma and persistent and proliferating cells of the theca interna (GEIST, GAINES & POLLACK, 1939).

Submitted for publication, May 18, 1953.

The histologic changes in the ovaries of irradiated mice have been described in detail by BRAMBELL et al. (1927), MURRAY (1931) and SNELL & AMES (1939), for example. FURTH & BOON emphasized that no clear line of distinction can be drawn between neoplasia and hyperplasia of the ovaries in such mice.

The production of estrogen is not completely suppressed in these mice. Vaginal smears continue to show the cytologic picture of estrus, although the latter is less regular. Persistent estrus rhythm is compatible with complete, histologically proved destruction of the follicular system (GEIST, GAINES & ESCHER, 1941). In irradiated guinea-pigs the excretion of estrogen in the urine is decreased, but irregular cycles do sometimes occur (SCHMIDT, 1936).

Ovarian tumours in mice sometimes metastasize (FURTH & BOON, 1945) and are transplantable (FURTH, 1946).

The mechanism involved in the development of ovarian tumours following roentgen irradiation is not properly understood. VOIGT (1938) suggested that overproduction of gonadotrophin by the hypophysis favours the development of granulosa cell tumours. LI, GARDNER & KAPLAN (1947) suggest that the roentgen rays may exert a direct carcinogenic effect. LICK et al. (1948) claimed hormonal imbalance to be an essential factor in the arisal mechanism of ovarian tumours following roentgen irradiation. They found that if only one ovary was irradiated (contact irradiation) and the other left untreated, the irradiation produced no tumour.

Experimental

The purpose of the present study was to check the effect of roentgen irradiation and to elucidate any rôle played by hormonal factors. Mice were roentgen irradiated and some of the animals were treated with estrogen to counteract any hyperproduction of hypophyseal gonadotrophin after irradiation, others received gonadotrophin in order to enhance the supposed gonadotrophic tumour-producing factor. The effect of irradiation and hormonal treatment was studied on vaginal smears. In order to find out the possible importance of irradiation of the hypophysis, the heads of some of the animals were protected by a lead screen during irradiation.

Female mice of a well-inbred but not homozygotic stock were used. In the beginning of the experiment the animals weighed about 15 gm and were 4—6 weeks old. Each animal, in a small cage, received a single dose (60 cm F. S. D., filter 0.5 mm Cu + 1 mm Al). The skin dose was measured with Sievert's ionization chambers. Under the experimental conditions used the dose received by the ovaries was practically the same as the skin dose. In some cases the heads were protected against irradiation

by a 2.5 mm thick lead screen. All of the animals were examined post mortem. The ovaries and any tumours were embedded in paraffin, sectioned and stained with haematoxylin-eosin.

In the first series the roentgen dose was found to claim a high mortality, besides which the irradiated animals could not tolerate estrogen well; the experiment was repeated therefore in a second series but with a smaller roentgen dose and less estrogen. This second series was studied mainly for the occurrence of estrus after irradiation and hormonal treatment.

Series 1. — All of the animals died spontaneously. Eighty-four mice were used as controls (C); 299 were irradiated, 150 over the entire body (B), 149 with the head protected (HB). The skin dose delivered was 335—505 r (average 415 r). A dose of 20 r was measured under the lead screen. The 150 mice that were irradiated over the entire body were divided into 3 equal groups. One group (B) received no hormonal treatment, while the second group (BE) received injections of estrogen (6.25 γ daily for 3 months and then 12.5 γ daily for the following 4 months). The remaining group (BP) received injections of chorionic gonadotrophin for 4 months (3 I. U. daily) as from one month after irradiation.

The 149 animals irradiated with the head protected were likewise divided into three groups. One group of 49 animals (HB) received no hormonal treatment; of the other two groups, one received injections of estrogen (HBE) (6.25 γ daily for the first month and 12.5 γ daily for the following four months); the third group (HBP) were treated with chorionic gonadotrophin in the same way as the BP animals.

Series 2. — Nine mice were used as controls (EC). Forty-one were irradiated all over with an average skin dose of 170 r (165—195 r). Of the irradiated mice (EB) nine (EBE) received injections of estrogen, 2.5 γ daily as from one month after irradiation, and 9 (EBP) received 10 I. U. chorionic gonadotrophin every other day during the same period, while the remainder, 23 (EB), received no hormonal treatment. All of the animals surviving after one year were killed.

Results

Series 1. — Mortality within the first few weeks of irradiation was high: 34 per cent of those irradiated all over and 18 per cent of those irradiated with the head protected died within one month. The corresponding figure for the controls was only 4 per cent (diagrams 1—3). The mortality among the irradiated animals which received gonadotrophin did not differ much from that among the animals which were treated with radiation only, while the early mortality among those treated with both estrogen and roentgen rays was much higher than among the other

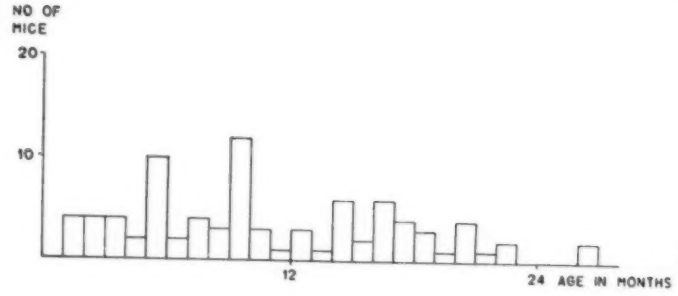

Diagram 1

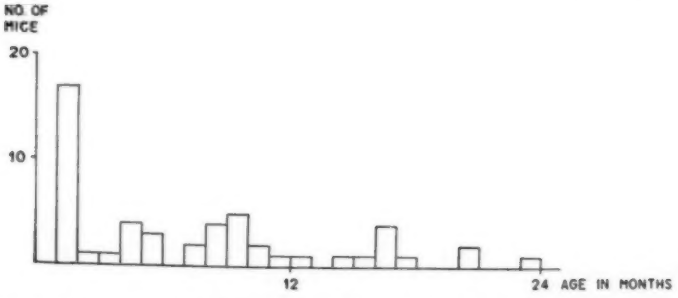

Diagram 2

Diagram 1 (above). Age-distribution of 84 control mice at time of death.
Diagram 2 (below). Age-distribution of 50 mice irradiated all over (about 400 r) at time of death.

animals (diagrams 6—7). Hardly any of the animals which had been treated with estrogen survived more than one year. The dose of estrogen administered and which produced permanent estrus, must have exerted a toxic effect. Purulent infections of the lungs and liver necrosis were common. In most of the animals, the kidneys, ureters and the urinary bladder were severely enlarged. Pyelonephritis was not uncommon. The vagina was markedly swollen and the uterine horns were thickened and sometimes filled with pus. Tumour-like pyovaria were common.

Spontaneous tumours (apart from leukaemia) were seen in 5 of the controls. Mammary tumours were recorded in 2 which died at 18 months and 26 months of age. Histologic examination showed infiltrating adenocarcinoma with pulmonary metastases in 1 of these, while in the other the tumour was built up of tubular formations with regular cells and probably of low malignancy. It was observed that in mice of this stock mammary carcinoma was capable of developing in animals older than 18 months: no such tumours were seen in any of the mice below this age. As 13 mice survived more than 18 months, the relative frequency of mammary car-

Diagram 3

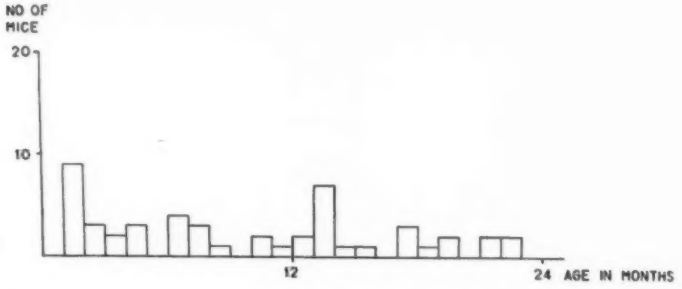

Diagram 4

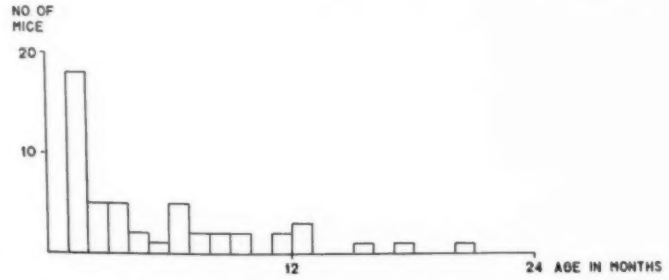

Diagram 3 (above). Age-distribution of 49 mice irradiated all over (about 400 r) with the hypophysis screened off.

Diagram 4 (below). Age-distribution of 50 mice irradiated all over (about 400 r) and treated with gonadotrophin.

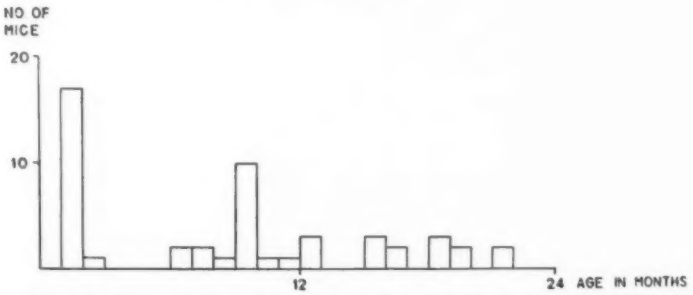

Diagram 5. Age distribution of 50 mice at time of death. The animals had been irradiated (about 400 r) all over with the hypophysis screened off and had been treated with gonadotrophin.

cinoma in this stock was 1 : 13 (calculated by the method of LEFÈVRE). Ovarian tumours were seen in 3 animals that died at 16, 19 and 20 months of age. As 23 of the animals survived more than 16 months the relative frequency of ovarian tumour was 3 : 23. In the animal that died at the

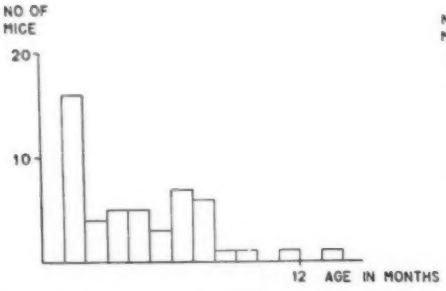

Diagram 6. Age distribution of 50 mice at time of death. The animals had been irradiated all over (about 400 r) and had received estrogen.

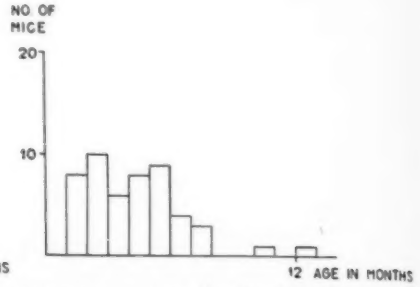

Diagram 7. Age distribution of 50 mice at time of death. The animals had been irradiated (about 400 r) with the hypophysis screened off and had received estrogen.

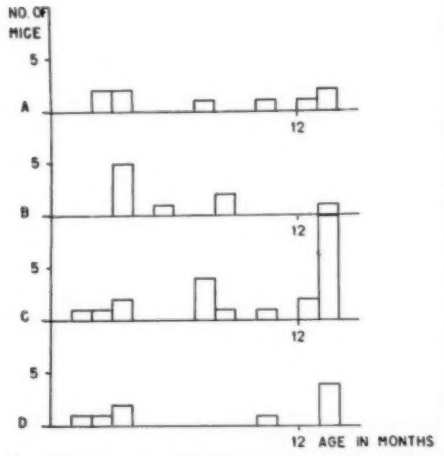

Diagram 8. Age distribution of 50 mice that had died or been killed. Series II: 9 mice irradiated all over and treated with gonadotrophin (A); 9 mice irradiated all over and treated with estrogen (B); 23 mice irradiated all over (170 r) (C) and 9 control mice (D).

age of 16 months a solid, brown reddish tumour ($5 \times 2.5 \times 3$ mm) was found in the left ovary. The other ovary was normal. Microscopic examination was not possible because of postmortal changes. In the animal that died at 19 months, one ovary was normal, while the other had degenerated into a bluish tumour measuring $2 \times 2 \times 3$ mm. Both the ovary and the tumour were richly vascularised. The uterine horns were enlarged as during estrus. The microscopic picture of the ovarian tumour showed granulosa cell proliferations of carcinomatous appearance. In the mice that died at 20 months of age the vagina and the uterine horns were enlarged. The ovaries were rounded, reddish blue, measured about $3 \times 2 \times 2$ mm and histologically resembled granulosa cell tumour of the trabecular cylindroid type seen in human beings (Fig. 1).

Among the animals that were irradiated all over an ovarian tumour was seen in one that reached the age of 17 months. A yellow white, solid

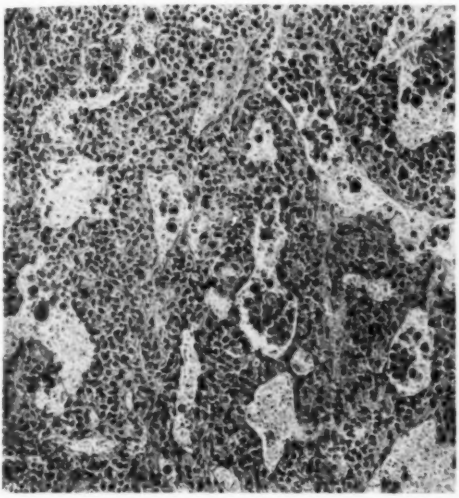

Fig. 1. Spontaneous granulosa cell tumour of trabecular-cylindroid type in mouse (× 200).

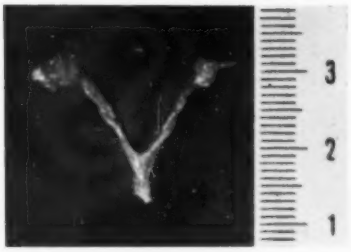

Fig. 2. Ovarian tumours in mouse irradiated all over.

tumour measuring 5 × 4 × 3 mm was found in the right ovary, and a similar one measuring 4 × 3 × 2 mm in the left (Fig. 2). Postmortal changes made microscopic examination impossible. The relative frequency of ovarian tumours in the animals irradiated all over was 1 : 4. In one animal that died at the age of 20 months papillary adenoma of the lungs was found. The relative frequency of pulmonary papilloma was 1 : 3. In the spleen of one animal that died at the age of 16 months, a large cavernous haemangioma was seen.

The following tumours were seen in the animals that were irradiated with the head protected: a mammary tumour with a histologic picture of lively infiltration — partly of cancer simplex type and partly of adenocarcinomatous appearance — was found in one animal that died at the age of 12 months. The relative frequency of mammary tumour was 1 : 21. A pulmonary adenoma was seen in one animal that died at 19 months, and a large pulmonary adenoma in one that reached the age of 22 months. The relative frequency of pulmonary tumour was 2 : 6. Ovarian tumours were demonstrated in animals that died at the ages of 11 and 19 months. The relative frequency of ovarian tumours was 2 : 22. The animal that died at 11 months of age had a firm, grey red tumour measuring 3 × 5 × 7 mm in the left ovary and a similar one measuring 4 × 3 × 2 mm in the right ovary. Postmortal changes made histologic examination impossible.

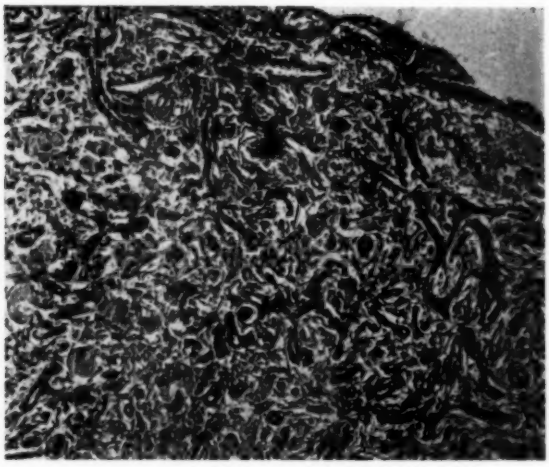

Fig. 3. Ovarian tumour with adenomatous tubular proliferation in a mouse irradiated (400 r) with the head screened off (× 100).

The animal that died at 19 months had a firm bluish red tumour measuring 2 × 2 × 1 mm in the left ovary; the microscopic picture was that of adenomatous tubular proliferation (Fig. 3). The vaginal mucosa showed signs suggestive of cornification.

Of the animals irradiated all over and treated with gonadotrophin a pulmonary adenoma was seen in one that died at 12 months of age (relative frequency 1 : 6) and a haemangioma was noted in the spleen of one that had reached the age of 17 months. No ovarian tumour was seen in this group.

Of those animals irradiated with the head protected and afterwards treated with gonadotrophin, pulmonary adenoma or pulmonary carcinoma was seen in 3 that died 9, 16 and 19 months of age, respectively. The relative frequency of pulmonary tumour was 3 : 27. An ovarian tumour was seen in one animal that died at 16 months of age. In the left ovary was a 2 × 2 × 1 mm firm, solid, white tumour and in the right was a similar tumour measuring 3 × 3 × 2 mm. The uterine horns were swollen as in estrus. The vagina showed extensive cornification and the ovaries, a microscopic picture of a tumour of uncertain type. The relative frequency of ovarian tumour was 1 : 9.

No tumour was seen with certainty in any of the animals irradiated all over and treated with estrogen. Of those animals irradiated all over but with the head protected and afterwards treated with estrogen, mammary cancer developed in one. The animal died at 12 months and had a tumour of partly undifferentiated and partly adenocarcinomatous structure. As only one animal in the group reached this age, the relative frequency of

ovarian tumour was 1 : 1. One animal, which died at 3 months, had a pea-sized cyst filled with mucus, in the right ovary. Microscopic examination showed papillary excrescences lined with cylindric epithelium with many mucus-producing cells.

The distribution of the tumours seen in series I is summarized in table I.

Table 1

Relative frequency of tumours in a) untreated, b) irradiated and c) irradiated and hormon-treated female mice. (Age at appearance of first tumour is given in brackets.)

Group	No. of mice	Mammary cancer	Ovarian tumour	Pulmonary tumour	Remarks
Controls	84	1/13 (18 months)	3/23 (16 months)	0	1 probably benign mammary tumour
Irradiated	50	0	1/4 (17 months)	1/3 (2) months)	1 splenic haeman-gioma
Irradiated with hypophysis screened off	49	1/21 (12 months)	2/22 (11 months)	2/6 (19 months)	
Irradiated and treated with gonadotrophin	5)	0	0	1/6 (12 months)	1 splenic haeman-gioma
Irradiated with the hypophysis screened off and treated with gonadotrophin	5)	0	1/9 (16 months)	3/27 (9 months)	
Irradiated and treated with estrogen	5)	0	0	0	
Irradiated with the hypophysis screened off and treated with estrogen	5)	1/1 (12 months)	0	0	1 ovarian cyst

Statistical analysis of the observations made showed that as far as the incidence of tumours was concerned the groups did not differ from one another in any way that could not be ascribed to chance. The difference between the observed frequency and the expected frequency of any single type of tumour was also due to chance. This does not, however, apply to pulmonary tumours: the difference in this case between the controls and the irradiated animals, especially those that were afterwards treated with gonadotrophin, is fairly large and may be reagarded as statistically probable, especially on comparison of the frequency of tumours in the corresponding age-groups. In the mice that received gonadotrophin the tumours showed a tendency to appear earlier than in the others.

It seems that those animals treated with estrogen died very early. GARDNER (1950), who studied the effect of estrogen and testosterone on the formation of ovarian tumours in irradiated mice, also reported a high

early mortality of the animals treated with estrogen, so that no valid conclusions can be drawn.

Atrophy and fatty degeneration and sometimes a certain proliferation of the germinal epithelium, occasionally forming invaginations or small cellular cords and tubules, in the cortex, were seen in the irradiated ovaries (B-animals) 1 year after irradiation. Later, increasing proliferation was sometimes observed from the germinal epithelium so that in some parts there was a cortex built up of tubular adenomatous tissue with small dark cells and isolated mitoses. In some areas there was, as before, fatty atrophic tissue which was now vascularized.

Not until the control animals were 650 days old were tubules seen in the ovaries. One 788-day-old animal showed gross, invaginating ducts extending from the slightly proliferating germinal epithelium in otherwise atrophic ovaries. The histologic structure of the irradiated ovaries thus resembled that of ageing ovaries, an observation also made by ENGEL (1946), who studied ovaries from very old mice.

Series 2. — Neither in those animals that died spontaneously nor in those controls killed at 13 months were any tumours found. Of the irradiated animals, one had an ovarian cyst and one a granulosa cell tumour at the end of the experiment. The ovarian cyst was the size of a pea and was filled with mucus. Some parts of its wall showed lowly differentiated epithelium, while other parts showed cylindric epithelium with scattered mucus-producing cells. The ovarian tumour, which was on the left side, was firm, measured 11 × 8 × 17 mm, and showed blue, red and yellow blotches. Microscopic examination revealed a trabecular cylindroid granulosa cell tumour with numerous mitoses in the tumour cells (Fig. 4). The other ovary was small. The uterine horns were enlarged as in estrus. The vagina had undergone extensive cornification. In none of the animals treated with estrogen did any tumour appear. Of those treated with gonadotrophin, one, which was killed at 13 months, had a pulmonary tumour.

The results of the analysis of vaginal smears from control animals, irradiated animals and animals irradiated and afterwards treated with gonadotrophin are summarized in table 2.

The dose delivered had thus not completely inhibited estrus. In the beginning, estrus was just as common in the controls as in the others. Ten weeks later, the frequency of estrus in the irradiated animals dropped considerably. The administration of gonadotrophin increased the frequency of estrus 4—10 months after irradiation *i. e.* 3—9 months after commencement of hormonal treatment, as compared with irradiated animals not afterwards treated with hormones. The animals in each group did not differ appreciably from one another regarding the frequency of estrus. Fertility

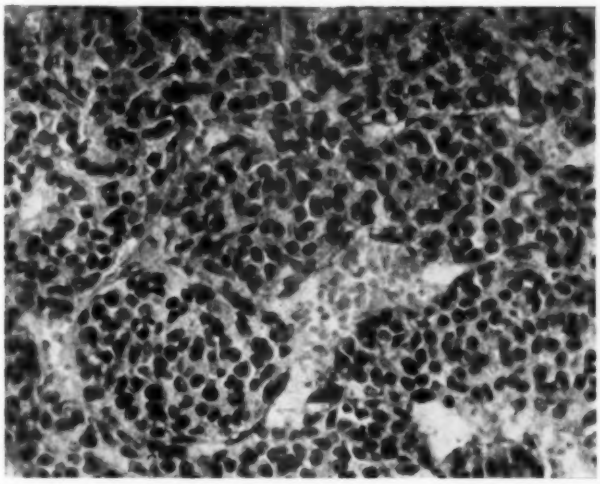

Fig. 4. Granulosa cell tumour in a mouse irradiated (170 r) all over (× 365).

tests were carried out 75 days after irradiation. All of the controls gave birth, but none of the irradiated animals. A dose of 170 r had thus not completely inhibited estrus, but the irradiated animals were evidently sterile at the time of the test.

In one irradiated animal which died 82 days after irradiation, the germinal epithelium was still low and single-layered. In another animal that

Table 2

Frequency of estrus in a) untreated, b) irradiated (170 r) and c) irradiated mice treated with gonadotrophin.

Time after irradiation	Number of animals examined and percentage of smears with signs of estrus	
30—40 days	7 control mice — 30 %	8 irradiated mice — 28 %
40—60 days	8 irradiated mice — 43 %	3 irradiated mice treated with gonadotrophin — 51 %
60—75 days	8 irradiated mice — 33 %	2 irradiated mice treated with gonadotrophin — 30 %
75 days—4 months	3 irradiated mice — 13 %	2 irradiated mice treated with gonadotrophin — 2 %
4—5 months	4 irradiated mice — 5 %	5 irradiated mice treated with gonadotrophin — 16 %
5—6 months	4 irradiated mice — 11 %	5 irradiated mice treated with gonadotrophin — 31 %
6—7 months	3 irradiated mice — 4 %	4 irradiated mice treated with gonadotrophin — 23 %
7—8 months	not examined	
8—9 months	4 irradiated mice — 5 %	4 irradiated mice treated with gonadotrophin — 34 %
9—10 months	1 irradiated mice — 0 %	3 irradiated mice treated with gonadotrophin — 26 %
9—10 months	2 control mice — 38 %	

died 183 days after irradiation, the germinal epithelium was cubical and stained readily, but had not yet formed tubules. Two hundred and eleven days after irradiation, isolated tubules were seen in the periphery of the ovaries, the major part of which had undergone fatty degeneration. Two hundred and eighty-nine days after irradiation the germinal epithelium formed single tortuous ducts and cellular cords in the cortex, which thereby assumed an adenomatous appearance. Three hundred and sixty days after irradiation, pale-staining cells with large nuclei were seen in the tubules. These ovaries showed a moderate degree of hyperaemia and the endometrium contained a moderate number of glandular structures. Of the animals treated with gonadotrophin and irradiated, even those that died about 220 days after irradiation showed this type of picture; the vagina was also cornified and the glandular tubules in the endometrium were numerous and some of them were dilated and cyst-like. It seems that gonadotrophic hormones produce increased 'activity' in irradiated mice. This supports the observations made by ESSENBERG (1949), who studied the effect of gonadotrophic hormones on the ovaries of irradiated mice. After administration of 300 r at the age of 3—4 weeks these experimental animals received 10—15 I. U. of RE gonadotrophin twice a week for 3 months. Other animals received a hypophyseal implantation once a week, likewise for 3 months. After this treatment the animals were admittedly still sterile, but when killed after the lapse of a further 3 months, the ovaries of those treated with gonadotrophin (and a few of those treated with hypophyseal implantation) showed higher germinal epithelium with more numerous mitoses; they also showed the presence of more numerous large, pale-staining cells in the cortex than did the controls.

The opportunity is taken of thanking Dr. L. SANTESSON, Radio-pathologic Institute, Stockholm, and Professor F. LINELL, Department of Pathology, Lund, for help with the histologic examination of the slides and Professor C.-E. QUENSEL, Department of Statistics, Lund, for assistance with the statistical analysis.

SUMMARY

Roentgen irradiation of 4—6 week old female mice with a dose of about 400 r produced no definite difference in the frequency of ovarian tumour or mammary carcinoma but increased the frequency of pulmonary tumour. In this respect irradiation of the entire animal had the same effect as irradiation with the hypophysis protected by a lead screen. The administration of gonadotrophic hormone to irradiated animals was followed by the increased occurrence of pulmonary tumour in earlier age. Administration of estrogenic hormone to irradiated animals claimed a high mortality.

Animals irradiated with about 170 r became sterile and the frequency of estrus from the tenth week to the tenth month after irradiation was low. Gonadotrophin treatment increased the frequency of estrus and histologic examination showed a tendency to increased activity in the ovaries of the animals treated in this way.

ZUSAMMENFASSUNG

Röntgenbestrahlung von 4—6 Wochen alten weiblichen Mäusen mit Dosen von ungefähr 400 r erzeugte keinen definitiven Unterschied in der Frequenz der Ovarialtumoren oder des Mammakarzinomes; die Frequenz der Lungentumoren wurde jedoch erhöht. In dieser Hinsicht hatte die Bestrahlung des ganzen Tieres den gleichen Effekt wie die Bestrahlung bei durch Blei abgeschirmter Hypophyse. Die Verabreichung gonadotroper Hormone an bestrahlte Tiere hatte ein vermehrtes Auftreten von Lungentumoren in jüngerem Alter zur Folge. Die Darreichung östrogener Hormone an bestrahlte Tiere rief eine hohe Sterblichkeit hervor.

Tiere, die mit etwa 700 r bestrahlt worden sind, wurden steril und die Frequenz der Brunstperioden war von der 10. Woche bis zum 10. Monat nach der Bestrahlung gering. Behandlung mit Gonadotropin steigerte die Frequenz des Oestrus und die histologische Untersuchung zeigte in den Ovarien so behandelter Tiere erhöhte Aktivität.

RÉSUMÉ

L'irradiation de souris femelles âgées de 4 à 6 semaines par les rayons de Roentgen à la dose d'environ 400 r n'a pas influé nettement sur la fréquence des tumeurs de l'ovaire ou des cancers de la mamelle, mais a augmenté la fréquence des tumeurs pulmonaires. A cet égard, l'irradiation totale de l'animal a eu le même effet que l'irradiation avec protection de l'hypophyse par un écran de plomb. L'administration d'hormone gonadotrophique aux animaux irradiés a été suivie d'une augmentation de fréquence des tumeurs pulmonaires dans le jeune âge. L'administration d'hormone oestrogénique aux animaux irradiés a entrainé une mortalité élevée.

Les animaux qui avaient reçu une dose d'environ 700 r devinrent stériles et, chez eux, de la dixième semaine au dixième mois après l'irradiation, l'oestrus fut peu fréquent. Le traitement par la gonadotrophine augmenta la fréquence de l'oestrus et l'examen histologique montra chez les animaux traités de cette façon une tendance à l'augmentation de l'activité de l'ovaire.

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FROM THE DEPARTMENT OF GYNECOLOGY (DIRECTOR: PROF. P. WETTERDAL), SABBATSBERGS SJUKHUS, KAROLINSKA INSTITUTET, STOCKHOLM, SWEDEN

A STUDY ON THE PROTECTIVE ACTION OF 2,3-DIMERCAPTOPROPANOL (BAL) ON RADIATION-INDUCED CHANGES IN THE OVARIAN FOLLICLES IN MICE

by

Erik Odeblad

In recent years the protective action of sulfhydryl-containing compounds on changes induced by ionizing radiations has been comprehensively studied. After the early reports by PATT and coworkers (1949), CHAPMAN and coworkers (1949) and BARRON and DICKMAN (1949), evidence has accumulated that sulfhydryl-containing compounds act as competitive acceptors for certain injurious products, such as hydroxyl- and perhydroxyl-radicals formed in irradiation of the tissue water in the presence of oxygen. It seems probable that some protection may be obtained in any tissue, provided that a sufficient sulfhydryl concentration can be established. The degree of protection cannot be predicted, however, and has to be studied experimentally. In this work the protection obtained with 2,3-dimercaptopropanol (BAL) on radiation-induced changes in the ovarian follicles in mice, has been studied.

In previous works (ODEBLAD, 1952, 7, 8), it was shown that a dosage of 3 μC/g of P^{32}-labelled orthosphate produced readily observable histologic follicular damage in mice (strain An 51) after four days, and that 10 μC/g caused extensive histologic damage. A dosage of 5 μC/g was chosen in this investigation in order to obtain a moderate effect. Preliminary studies have shown that 400—600 r total body irradiation with 165 kV roentgen rays gives comparable ovarian changes. The dose 600 r is about the LD-50—10 days for this strain.

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Experimental

A total of 146 adult healthy female virgin mice of the strain An-51 were used. They were divided into the experimental groups given in Table I.

Table I

Experimental treatment of animals

Group	Number of animals	Injection of oil	Injection of BAL	Injection of P^{32}	Roentgen irradiation
A 1	20	—	—	—	—
A 2	10	++	—	—	—
A 3	10	+	—	—	—
A 4	10	++	++	—	—
B 1	20	++	—	5 μC/g	—
B 2	16	++	++	5 μC/g	—
C 1	10	+	—	—	400 r
C 2	14	+	+	—	400 r
D 1	10	+	—	—	600 r
D 2	14	+	+	—	600 r
E	12	—	—	3 μC/g	—

+ denotes injection of 0.15 ml arachis oil plus 2 per cent benzyl benzoate one hour before roentgen irradiation, or injection at the same point of time of the same solution containing 1.5 mg BAL.

++ denotes repeated injections of the same solutions, the first — one hour before the injection of P^{32} and then every twelve hours until the death of the animal.

P^{32} was given as orthophosphate in 0.3 ml of distilled water with 0.05 mg carrier, subcutaneously behind the head.

Roentgen irradiation was given from a tube at 165 kV and 6 mA, focus-skin distance 40 cm, filter 0.5 mm Cu + 1 mm Al. The dosage rate was about 36 r/min.

By comparing Groups A1, A2, A3 and A4 it was possible to decide if the oil solutions or the BAL had any influence on the ovaries. By comparing Groups B1 and B2 it was possible to see if BAL had any protective action on the changes induced by beta-irradiation, and by comparing Groups C1 and C2 and Groups D1 and D2 it could be determined whether BAL had any protective action on the changes induced by roentgen irradiation. Group E was added later to determine the degree of protection given by BAL on beta-irradiated mice.

The animals were examined daily, the body weight and the vaginal smears being recorded. Four days after the injection of P^{32} and four or six days (see Table I) after the exposure to roentgen radiation, the animals were killed with ether and the ovaries were rapidly removed and fixed in 6 per cent formalin plus 5 per cent trichloracetic acid, embedded in paraffin and cut into sections 4 μ thick. One true central section of each ovary was selected for measurement of the apparent diameters of

the follicles, which has been shown to be a reliable method for quantitative radiobiologic measurements in this mouse strain (ODEBLAD, 1952, II). Sections from Groups B1 and B2 were placed on methacrylate slides and autoradiographed with Gevaert non-screen roentgen ray film over a period of 10 days. Development was carried out in G 209 A for 4 minutes at +19° C. A total of 116 ovarian autoradiographs were studied.

Results

The general condition of the animals

The general appearance of the animals in Groups A1, A2 and A3 was about the same. In Group A4 it was seen that the BAL had caused a reduction of weight and the occurrence of general constitutional disturbance, tremors and spasms. In Groups B1, C1 and D1, weight loss and other signs of the radiation syndrome occurred with no significant difference from Groups B2, C2 and D2. The weight loss in Group E was less than that in group B1.

On autopsy no general macroscopic differences were seen between the various groups. The spleens in the Group B1 were somewhat engorged and those in Groups C1, C2, D1 and D2 were considerably reduced in size.

The vaginal smears

No definite conclusions regarding the ovarian function could be drawn from observations on the vaginal smears, partly because irregular cell forms occurred and partly because the duration of the experiment was too short.

The macroscopic appearances of the internal genital organs

The uteri and ovaries in Group B1 appeared somewhat more reduced in size compared with those in the other groups. Young corpora lutea were infrequent in Group B1.

The microscopic appearances of the internal genital organs

No definite signs of estrogen deficiency could be seen in the uteri in the irradiated groups.

The ovaries of Groups A1, A2, A3 and A4 presented quite normal histologic appearances. In Group B1, changes resembling those described earlier (BLOM, 1948, WARREN, MC MILLAN and DIXON, 1950, ODEBLAD, 1952, 7, 8) were frequently seen in the follicles. In Group B2, these changes were less pronounced and were similar to that produced by the lesser dose of beta-irradiation employed in Group E. In Groups C1, C2, D1 and D2, the corresponding changes were not suggestive of protection.

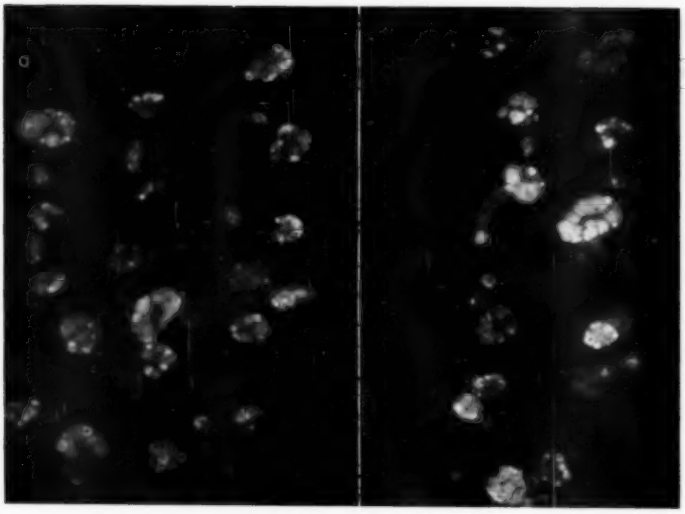

Fig. 1. Autoradiographs from Groups B1 (left) and B2 (right). The amount of radiophosphorus (white) is greater in B2 than in B1. Magnification: × 5.

Table II

Results of measurements of follicular diameters

Group	Average follicular diameter microns	Number of follicles investigated
A1	152 ± 5	334
A2	149 ± 7	157
A3	157 ± 6	165
A4	160 ± 6	160
B1	94 ± 5	402
B2	134 ± 6	292
C1	108 ± 6	205
C2	120 ± 8	302
D1	92 ± 6	210
D2	109 ± 7	183
E	131 ± 6	181
		Total 2,591

Measurements of follicular diameters

According to earlier results (ODEBLAD, 1952, 8), the measurement of follicular diameters is the most reliable measure of ovarian radiobiologic damage in mice. The mean follicular diameters were about the same in Groups A1, A2, A3 and A4 (see Table II).

As regards continuous beta-irradiation, a considerable reduction occurred in Group B1. In Group B2, the mean diameter was significantly different from that of B1 and was similar to that in Group E. That means that after the administration of 5 μC/g P^{32}, protection due to the BAL has occurred and that this protection is of an order of magnitude resulting in a damage ordinarily caused by 3 μC/g of P^{32} (or about 40 per cent protection).

A considerable reduction of follicular diameters was obtained in Groups C1 and D1 by single doses of roentgen rays. As the mean diameters in Groups C2 and D2 did not differ significantly from those in C1 and D1, there was no significant protection by BAL against the roentgen irradiation administered.

Autoradiographic observations

When comparing autoradiographs from Groups B1 and B2, the density corresponding to the follicles (and probably also the corpora lutea) were higher in Group B2. Grain countings on the follicles indicated that the exposure from the granulosa tissue was 30 $\pm$ 12 per cent higher in Group B2 than in Group B1 (fig. 1). This is to be expected if the depression of ribonucleic acid resynthesis (HEVESY, 1946, HOLMES, 1949, KELLY and JONES, 1950) is protected by BAL.

Discussion

From the results of this investigation it is evident that the changes produced by P^{32} in the ovaries may be partially protected by BAL given repeatedly during the course of internal irradiation. In the case of roentgen rays of comparable doses, protection to similar degree was not found.

The cause of this difference may be manyfold. It may depend on differences in the mean specific ionization between beta-rays and roentgen rays, though this is not very probable. The beta-irradiation was delivered continuously during 4 days and was accompanied by the injection in all of 8 times as much BAL as in the case of roentgen rays, which were delivered in 11 or 16 minutes. Finally, it may depend on the fact that the roentgen irradiation is distributed more uniformly to the body than the beta irradiation which is more selective for certain organs taking up much P^{32}.

The most important implication of this investigation is that a specific organ has been proven to be protected during continuous irradiation over several days. This may be practically utilized in cases of overdosage of radioisotopes given internally and in cases of accidental poisoning by their ingestion. Less toxic sulfhydryl compounds than BAL may also be tried in such cases. Further investigation of this problem is required for its satisfactory solution.

SUMMARY

Mice were given internal irradiation with P^{32} (5 μC/g) and external total body irradiation with roentgen rays (400 or 600 r). Some of the animals were treated with 2,3-dimercaptopropanol (BAL). The animals were sacrificed after 4 or 6 days. Follicular diameters in the ovaries were measured and grain countings were undertaken on ovarian autoradiographs.

Significant protection (estimated to be about 40 per cent) was obtained against irradiation effects with the BAL in the P^{32}-treated animals. No significant protection was obtained in the roentgen irradiated mice. This may be due to the fact that repeated injections of BAL were given in the P^{32}-irradiated mice, but only one injection of BAL in the roentgen irradiated mice. Treatment of radioisotope intoxication by means of sulfhydryls is suggested.

ZUSAMMENFASSUNG

Mäuse wurden mit P^{32} (5 μC/g) intern bestrahlt und erhielten externe Totalbestrahlung mit Röntgenstrahlen (400 r oder 600 r). Einige dieser Tiere wurden mit 2,3-Dimercaptoproponal (Bal) behandelt. Die Tiere wurden nach 4 oder 6 Tagen abgetötet. Die Durchmesser der Ovarialfollikel wurden ausgemessen und Körnchenzählungen an Ovarialautoradiographien vorgenommen.

Signifikativer Schutz gegen die Strahlenwirkungen (schätzungsweise um 40 %) wurde mit Bal bei den mit P^{32} behandelten Tieren erreicht, dagegen nicht bei den röntgenbestrahlten Mäusen. Das mag auf der Tatsache beruhen, dass den mit P^{32} bestrahlten Mäusen mehrere Bal-Injektionen verabreicht wurden, während die röntgenbestrahlten Mäuse nur eine Einspritzung mit Bal bekamen. Die Behandlung der Intoxikation durch radioaktive Isotope mit Hilfe von Sulphhydrylen wird vorgeschlagen.

RÉSUMÉ

Des souris furent exposées, les unes à une irradiation interne par le P^{32} (5 μC/g), les autres à une irradiation externe de tout le corps par les rayons roentgen (400 ou 600 r). Certains de ces animaux furent traités par le 2,3-dimercaptopropanol (BAL). Les animaux furent sacrifiés au bout de 4 ou 6 jours. Le diamètre des follicules ovariens fut mesuré et les granulations comptées sur les autoradiographies des ovaires.

Le BAL a donné une protection importante (estimée à environ 40 %) contre les effets de l'irradiation chez les animaux soumis au P^{32}, mais pas de protection appréciable chez les souris soumises aux rayons roentgen. Ceci peut être dû à ce que les injections de BAL ont été répétées chez les souris soumises à l'irradiation par le P^{32}, et uniques chez les souris soumises aux rayons roentgen. L'auteur suggère de traiter l'intoxication par les radio-isotopes par les sulfhydryles.

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FROM THE RADIUM CENTRE FOR JUTLAND AND THE ROENTGEN DEPARTMENT (DIRECTOR: PROFESSOR CARL KREBS) OF THE MUNICIPAL HOSPITAL, AARHUS, DENMARK

SYMPATHICOBLASTOMA OF THE ADRENAL MEDULLA WITH OSSEOUS METASTASES

A Report of Three Cases Including One Surviving Eleven Years after Roentgen Therapy

by

Poul Bjerre Hansen

In 1942, TH. ROSENDAL (15) reported in this journal two cases of sympathicoblastoma of the adrenal medulla in children. In both cases definite bone metastases were present, and the patients were treated with roentgen irradiation. The first patient, an 18-month-old boy, died about 12 months after the onset of the disease. The roentgen therapy had only a transitory beneficial effect. The second patient, a 12-month-old boy, was alive at the time of the report, about six months after the onset of symptoms. After the roentgen treatment there were certain signs of improvement but also of progression, so that the prognosis was regarded as very grave. However, this latter patient survived and has been under observation at the Radium Centre for Jutland during recent years. As it must be presumed that, in spite of the presence of bone metastases, a cure has been effected by the irradiation treatment given in 1941—42, it seems justifiable to present a description of the later course of this case in continuation of ROSENDAL's report of 1942. At the same time two additional cases of sympathicoblastoma in children treated in this hospital during recent years are reported. Both these patients died. Finally, the therapeutic possibilities are discussed in some detail.

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Report of Cases

Case 1. (3288/51.) A boy, aged 12 months (= ROSENDAL'S case 2).

According to *Rosendal's report*, the disease began in August 1941 (at the age of 7 months) with swelling of both temporal regions and protrusion of the eyeballs, most pronounced on the left side. On admission (to the Pediatric Clinic of the State Hospital, Copenhagen) in October 1941, a large abdominal mass was palpated, extending from the right costal margin to the right iliac crest. Roentgenograms of the skull revealed a distinct adiating spicule formation ("sunray" configuration) in the frontotemporal swellings. In the lateral portions of the frontal bone and posteriorly in the parietal bone on both sides, numerous small bilaterally symmetrical areas of rarefaction were seen. Similar changes were found in the right side of the mandible. The remainder of the skeletal system was uninvolved. Roentgen examination of the abdomen showed a soft-tissue shadow, the size of half a grapefruit, occupying the greater part of the right lumbar region.

A series of other examinations were uncontributory, and apart from a moderate anemia the general condition was fairly good. Histologic examination of a biopsy specimen from one of the temporal swellings showed *sympathicoblastoma* (Teilum).

Roentgen irradiation was given to the left and right temporal regions, 900 and 600 r, respectively, and to the right side of the abdomen and the right flank, 950 r in all (concluded January 1942). During the next few months the general health improved, the hemoglobin level rose, and the swellings of the temporal regions and the protrusion of the eyeballs subsided. A slight displacement of the left eye and some convergent strabismus persisted. Roentgen examination showed that the spicule formation had disappeared, whereas the destructive processes in the frontoparietal region had become more conspicuous, and that a large number of small, spotted, more or less confluent calcifications had developed in the abdominal tumor which had regressed somewhat on the right side but now extended a little to the left of the first lumbar vertebra.

A renewed course of roentgen treatment with somewhat smaller doses was given during April and May 1942, following which the patient was discharged.

In 1946, the child, who had been well in the meantime, was admitted to the Central Hospital, Randers, for some peculiar 'bumps' in the cranial wall, which had developed slowly during the past year.

Roentgen examination of the skull:

Corresponding to the 'bumps' in the right parietal region, there was considerable bulging of the almost paper-thin cranial wall. In the orbital and temporal portions of the frontal bone on both sides distinct sclerotic areas of a streaky appearance, studded with small irregular osteolytic spots, were noted, but there was no sign of the spicule formation. Roentgenograms of the abdomen showed an oblong soft tissue shadow with numerous large, spotted and partially confluent calcifications extending from the twelfth rib to the iliac crest along the right side of the spine, at the level of the first lumbar vertebra crossing the spine and reaching the upper pole of the left kidney (N. LAUGE HANSEN).

Several courses of roentgen treatment, totalling 1,800 r to three fields, were given to the swellings in the cranial wall. The 'bumps' receded somewhat, but did not disappear completely. The general health was good, and the only complaint during the next few years was a slowly progressive impairment of vision. In 1948, an ophthalmologic examination showed bilateral atrophy of the optic nerve head; vision 6/36 + 2.00 on both sides (PETER JENSEN).

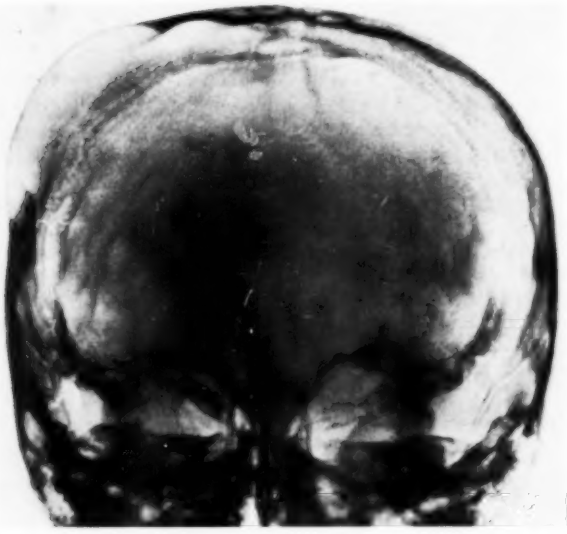

Fig. 1.

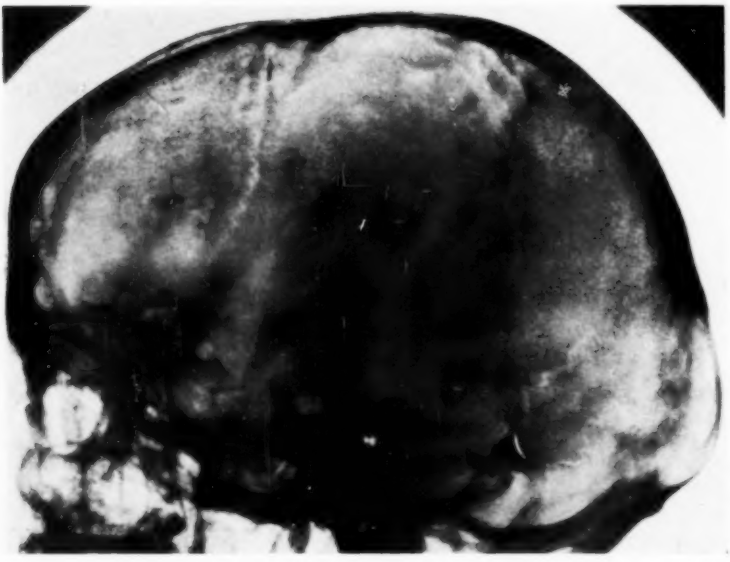

Fig. 2.

Figs. 1 and 2. Destructions of the lamina interna and corresponding bulging of the lamina externa in the occipital and parietal bones; alternating sclerosis and areas of rarefaction in the frontal and sphenoid bones.

As the bulgings in the cranial wall again increased in size, and the vision was further impaired, especially in the left eye, the patient was admitted to the Department of Neurosurgery in September 1951, and a few days later transferred to the *Radium Centre*.

The patient, then aged $10^1/_2$ years, was of slender build. Height 131 cm, weight 25 kg (normal 134 cm and 30 kg), but otherwise of normal development. Mental development was also considered normal, although the child was obviously marked by the chronicity of the disease and the considerably impaired vision. The skull was deformed by several osseous protrusions, especially in the right temporoparietal and the occipital regions. In the left temporal region, a somewhat more flat prominence was present. The circumference of the skull was 53.5 cm (normal 52 cm). The abdomen was soft, without definite palpable masses. There was no enlargement of peripheral lymph nodes.

Ophthalmologic examination. Slight convergent strabismus of the left eye; normal motor function; sharp-edged atrophy of both optic nerve heads. Vision: L. E., patient could count fingers at 4 m., R.E., 6/24 (VIGGO JENSEN).

Roentgen examination. (Figs. 1 and 2.) The changes in the cranial wall were essentially the same as observed at the previous examination. In and around the ceiling of the orbits, sclerotic areas with densities and occasional small rarefactions were seen. The changes were most pronounced on the left side, where they extended into the zygomatic process and backwards into the sphenoid bone. The sella turcica was not enlarged, but the left anterior clinoid process was deformed. In the remainder of the skeletal system involvement was found in two or three ribs, the left scapula, certain vertebrae and areas of the pelvis, which all showed isolated small rounded spots of lessened density surrounded by marked sclerosis. The lungs showed nothing abnormal. The partly calcified soft-tissue process in the abdomen had the same appearance as at the earlier examination (Figs. 3 and 4). The right kidney was displaced slightly downward and anterolaterally, whereas the left kidney was normal in position. No change of the pelvis, calyces or ureter. (A detailed discussion of calcifications in adrenal neoplasms has been given by SAMUEL (16) and MANDEVILLE (13)).

Other examinations: Diuresis: normal; no albuminuria or glucosuria. Blood urea 26 mg%. Hemoglobin 85 %. S. R. 6 mm/hour. Normal blood picture. Serum cholesterol 113 mg%.

In view of the history and the observations described, the clinical diagnosis was one of a calcified adrenal tumour with sclerotic, probably healed metastases. Any opinion as to the nature of the peculiar swellings in the cranial wall was somewhat uncertain, and a short course of roentgen therapy (a total of 500 r to four small fields) was instituted. *A biopsy specimen* from the occipital intumescence was removed. Under the very thin shell of bone was a soft, spongy, uncharacteristic tissue, which on histologic examination proved to consist of connective tissue poor in cells and vessels and without any evidence of active pathologic processes (W. MUNCK). Treatment was discontinued and the patient discharged. Immediately after the treatment the 'bumps' decreased a little in size but have since remained stationary. During the last two years the boy has been completely well; his severe impairment of vision must be considered permanent, and he is now in a school for the blind.

Case 2. (1466/46.) A boy, aged 18 months, had had measles without complications at the age of 4 months. In January 1946, at the age of 13 months, progressive weakness and fatigue developed. Some months later he was admitted to the regional hospital with considerable protrusion of the right eye, which had developed during the past few weeks. The patient was transferred to the Department of Neurosurgery and from there to the Radium Centre for observation for leukemia.

Fig. 3.

Fig. 4.

Figs. 3 and 4. Scattered calcifications in the right renal region and displacement forwards, downwards and slightly laterally of the right kidney.

The patient was severely affected and anemic with marked protrusion and displacement, particularly downwards, of the right eye, accompanied by keratitis, chemosis and conjunctivitis (fig. 5). The eye could only be moved slightly inwards and downwards and the pupil was slightly dilated. Ophthalmoscopic examination revealed normal conditions. The left eye was normal. The skull was large and characterized by slight hydrocephalus with a distinct venous pattern. On the left side of the abdomen, roughly corresponding to the spleen, was a large rather firm tumor, extending 5 cm below the costal margin and almost to the midline. Moderate enlargement of the peripheral lymph nodes was noted.

Roentgen examination. The skull revealed blurred digital impressions but no separation of the sutures. There was an indistinct, ill-defined destruction, 2 × 3 cm, in the right frontotemporal region. The sella turcica was normal. The thorax, pelvis and extremities did not reveal any osseous abnormalities; the lungs showed normal conditions.

Blood examination. Hemoglobin 60 %. Leukocytes 6,500; differential count: lymphocytes 71 %, monocytes 11 %, neutrophils 16 %, and eosinophils 2 %; no abnormal cells.

Biopsy specimens were secured by aspiration from a lymph node, the sternal marrow and from the tumor in the splenic region. Cytologic examination of these specimens revealed a fairly uniform picture with a large number of small round cells with dark, very sparse basophile cytoplasm. Apart from these cells, few other cell types were present. A few slightly larger, more immature cells of the same type were seen, especially in the bone marrow, where the hematopoietic tissue was markedly displaced. In addition to the cellular elements, large amounts of 'fibrillar cell debris' were present in all the speci-

mens. The cell type observed could not be determined with certainty, and it could only be said that it was a malignant blastomatous lesion. None of the abnormal cells were present in the peripheral blood. At a renewed examination, post mortem, it was realized that the fibrillar elements which had at first been regarded as cell debris actually belonged to the cells, and that these were sympathicoblasts with small axis cylinders (J.BICHEL).

Roentgen irradiation, totalling 650 r, was given to the right orbit through anterior and lateral fields. No beneficial effect was obtained; the course continued downhill, and the patient was transferred to the regional hospital at the parents' request, where death ensued a few days later.

Autopsy findings: Tumor of the left retroperitoneal region with metastases to lymph nodes, the skull, spinal column and ribs; anemia.

Histologic diagnosis: Sympathicoblastoma (VESTERDAHL JØRGENSEN).

Fig. 5. Exopthalmos and severe chemosis of the right eye with a swelling in the right frontal region.

C a s e 3. (926/50.) A boy, aged 5 years, had been in good health until the onset of the present illness, which began suddenly with stiffness of the neck and back, accompanied by pain in the legs, headache and fever. He was admitted to the regional hospital with a diagnosis of encephalomeningitis. However, a spinal fluid examination did not reveal any abnormalities (cf. WAHLGREN and RUDBERG's case, where a diagnosis of poliomyelitis was made at the onset of the disease (19)). The sedimentation rate was well over 100 mm/hour. The Widal, Wassermann and tuberculin reactions were negative. Moderate anemia; no signs of leukemia. The patient was given antibiotics, light treatment and cod-liver oil. For the next two months he was relatively well but then again deteriorated, with pain in the extremities, fatigue and progressive anemia, and a hard subcutaneous tumor developed in the left parietal region. He was readmitted to hospital, and roentgenograms of the skull, thorax and spine revealed numerous small areas of bone destruction. The lesions were bilaterally symmetrical and conferred a peculiar 'moth-eaten' appearance on the osseous structures, especially of the skull. Furthermore, histologic examination of tissue from the tumour of the scalp showed that it was of a sarcomatous nature and had possibly arisen from the nervous system. A diagnosis of *sympathicoblastoma* was suggested, although it could not be established with certainty (TAGE LUND).

The boy was then transferred to the Radium Centre for treatment. He was severely affected, pale and weak. The head was strikingly large, due partly to hydrocephalus and partly to the presence of several large, hard, flat subcutaneous prominences. There was moderate convergent strabismus of the right eye, but no exophthalmos. The movements of the eye were normal and vision was unimpaired. There was moderate generalized enlargement of the lymph nodes. No definite abdominal masses were palpable.

Roentgen examination. The skull was large, hydrocephalic, with separated sutures, widening of the sella turcica and numerous small, partially confluent areas of rarefaction. In the ribs, clavicles, throughout the pelvis, and in several vertebrae there were similar

widespread, symmetrically distributed areas of bone destruction. In the proximal ends of both humeri and femora similar changes were seen, but here the areas of destruction were larger and more confluent. Roentgen examination showed a soft-part opacity, the size of an orange, without calcification, in the right upper part of the abdomen. The right kidney was, perhaps, displaced slightly downwards, otherwise no urographic changes. As compared with the roentgenograms taken a month previously, the osseous metastases showed marked progression, and the separation of the cranial sutures had occurred during that month.

Roentgen treatment (a total of 500 r to two fields) directed to the skull, was instituted. Further therapy had to be abandoned because of rapid deterioration of the general condition. High fever developed, the anemia increased, and death followed a week later.

Autopsy findings: Tumor of the right adrenal gland. Metastases in lymph nodes, the liver and various bones. Severe anemia. Internal hydrocephalus.

Histologic diagnosis: Tumor tissue of a very immature and undifferentiated character, arising from nervous tissue: neuroblastoma or sympathicoblastoma (TAGE LUND).

Both individually and, particularly, taken together, these three cases of sympathicoblastoma arising from the adrenal medulla give a rather characteristic impression of the symptomatology of this group of diseases in conformity with the current conception of the condition. Only a few points need further mention. As reported, metastases both in the liver and bones were present in case 3, *i. e.*, a mixed form of the two types of the disease, the Pepper type and the Hutchinson type, formerly regarded as distinct varieties, was present. However, during recent years several similar cases have been reported, and it now seems generally agreed (*e. g.*, FARBER (7); KARSNER (11)) that there is scarcely any actual difference between them, although it may, perhaps, be practical to retain the two designations for the purpose of clinical description. It is well known that the osseous metastases show a predilection for the skull, especially for the orbital regions, as was also seen in the three cases reported here, although to a variable degree. The sympathicoblastomas share these sites of predilection, for example, with the chloromas and granulomas of Hand-Schüller-Christian's disease; it is, as BOYD (3) says, well to examine the abdomen when proptosis develops in a young child. It is obvious that urography is an important method of examination as the adrenal sympathicoblastomas often involve the urinary tract (9), and although not performed in any of the cases reported here, the method of pneumoradiography of the retroperitoneal space (RIVAS (14)) should also be borne in mind. Finally, it may be mentioned that a study of the bone marrow is a very valuable diagnostic aid. Bone marrow aspiration is relatively simple, and as metastases in the bones are very frequent, tumor cells may often be revealed by this method. Unfortunately, in the cytologic diagnosis it may be difficult to differentiate sympathicoblastoma from the blast leukemias, which in themselves offer differential diagnostic

difficulties. The importance of bone marrow biopsy has been emphasized, for example, by KATO and WACHTER (15) and is strongly recommended by the Norwegian investigators BERGAN (1) and THO (18), whereas others have found that the difficulties involved are so great that they do not rely on the results (WISSLER (15), GREENTHAL and EPSTEIN (15)). As reported in case 2, the cytologic bone marrow picture was plain enough when the possibility of sympathicoblastoma was called to mind. As also appears from this case, biopsy specimens aspirated from lymph nodes and from the tumor may also be a valuable diagnostic aid.

For an extensive review of the clinical, roentgenographic and pathologic characteristics of sympathicoblastoma and its differential diagnosis the reader is referred to ROSENDAL's paper (15) on these subjects. Only the therapeutic possibilities and the prognosis will be discussed here.

Up to the early 1940's it was generally agreed that the prognosis of sympathicoblastoma was extremely grave, the disease running a rapid and fatal course of a few months (BLACKLOCK, 1934 (15); REDMAN et al., 1938 (15)). In spite of the considerable radiosensitivity of these tumors, roentgen irradiation seems to have only a temporary effect. ROSENDAL found only two cures among the approximately 300 cases published up to 1940. In one of these, the patient was alive and well more than 15 years after the tumor had been removed (LEHMAN, 1917, 1932 (15)). In the second, the patient was free from recurrence more than two years after the roentgen treatment (WISSLER, 1940 (15)). In addition, CUSHING and WOLBACH (1927 (4)) reported a case, in which spontaneous recovery seems to have occurred due to a differentiation of the malignant cells in a normal direction, resulting in transformation into benign ganglioneuroma cells.

After the publication of FARBER's study from 1940 (7), amplified by WYATT and FARBER in 1941 (21) and continued by WITTENBORG's review from 1950 (20), views have changed somewhat for the better with regard to the therapeutic possibilities and the prognosis. These three studies all originating from the Children's Hospital, Boston, comprise a total of approximately 150 patients and show that cure, *i. e.*, absence of recurrence for 3 years and often for 8—12 years, was obtained in 25—30 per cent of the cases, which were treated surgically or with irradiation therapy.

Complete excision of the tumor gave a good prognosis (about 60 per cent cures in WITTENBORG's review). If tumor tissue was left behind at the operation, irradiation was instituted as soon as possible, preferably on the day of operation. This combined therapy also offered a good prognosis (again about 60 per cent cures). In all cases with metastases, irradiation was used as the only therapeutic measure, being directed both to the primary tumor and the metastases. The authors recommended that the total doses should be moderate, and that the irradiation should

be fractionated in comparatively small daily doses and be repeated once or twice at intervals of about three months. For further details the reader is referred to WITTENBORG's paper. The results of irradiation varied somewhat. In six patients with metastases to the liver, cure was obtained in all, whereas the presence of metastases in bones invariably resulted in a fatal course within one year, although good palliative effect was often obtained. However, FARBER claimed emphatically that irradiation treatment should nevertheless be tried in all such cases.

Case 1 reported here confirms the justification of this view. When the disease was recognized in 1941, the patient had unquestionable metastases in the skull. These metastases, as well as the primary tumor, were given roentgen treatment, and the child is still alive 11 years later, without evidence of recurrence. The extent of the treatment roughly corresponded to that recommended by FARBER, WYATT, and WITTENBORG. (FARBER's and WYATT's reports of 1940—41 were not known in Denmark in 1941.) In this patient healing has occurred, presumably with calcium deposits both in the primary tumor and in the metastases. There may have been several small osseous metastases which did not receive any irradiation, but nevertheless, these also have healed. A similar 'remote effect' has previously been observed in cutaneous metastases, which disappeared during the treatment of the primary tumor (WISSLER (15)). On the whole, there seems occasionally to be a tendency to spontaneous healing or, more precisely, to maturation of the tumor cells, resulting in a benign ganglioneuroma. As already mentioned, such a development was observed in a case reported by CUSHING and WOLBACH (4), and in FARBER's and WITTENBORG's series there were two patients with histologically verified sympathicoblastomas who recovered spontaneously (survival times 12 and 16 years), probably because of such a development in benign direction. On the other hand, a third patient lived 10 years without any treatment before osseous metastases developed. Thus, the metastases may apparently be latent for long periods. Hemorrhages, necrosis and calcifications are also considered to play a prominent part in the healing processes.

In addition to these large series from Boston, many reports on single or a few cases (*e. g.*, 1, 2, 5, 8, 12 and 18) have been published during the last 10—12 years, and in 1951 a review of 31 cases from the Los Angeles Children's Hospital was published. Most of these cases had extensive metastases, particularly in bones, and terminated fatally. As was also seen in the series from Boston, the prognosis for this category of patients is very grave. Attempts have also been made to treat sympathicoblastoma with radioactive substances, nitrogen mustards, etc., but according to the reports, the results have not been very promising (6, 10, 20). For the present it must be assumed that in the presence of a local primary tumor, surgical methods represent the most rational form of therapy, whereas

all other cases should be treated with roentgen irradiation, even when extensive metastases have developed. At any rate, the palliative effect is always valuable, and the course of the disease in the first of the cases reported seems to indicate that growth, both of the primary tumor and of the bone metastases, can be successfully arrested.

SUMMARY

Three cases of metastasizing sympathicoblastoma arising from the adrenal medulla are reported. One of these cases is felt to be exceptional because this child survived for eleven years after roentgen therapy despite the presence of widespread osseous metastases. A few comments are made on the diagnosis and symptomatology. Therapeutic measures and the prognosis are discussed in some detail.

ZUSAMMENFASSUNG

3 Fälle mit von der Nebennierenrinde ausgegangenen metastasierenden Sympathikoblastomen werden berichtet. Einer dieser Fälle wird als aussergewöhnlich angesehen, weil das Kind trotz vorhandener ausgedehnter Knochenmetastasen nach Röntgenbehandlung 11 Jahre lang lebte. Kurze Kommentare über die Diagnose und die Symptomatologie werden gemacht.

Therapeutische Massnahmen sowie die Prognose werden ziemlich eingehend besprochen.

RÉSUMÉ

L'auteur présent trois cas de sympathicoblastome métastatique provenant de la médullaire surrénale. Un de ces cas paraît exceptionnel en raison de la survie de l'enfant pendant onze ans après la radiothérapie, malgré la présence de métastases osseuses disséminées. L'auteur fais quelques commentaires sur le diagnostic et sur la symptomatologie et étude de façon assez détaillée les mesures thérapeutiques et le pronostic.

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FROM THE ROTTERDAM INSTITUTE OF RADIOTHERAPY, ROTTERDAM, HOLLAND

SPONTANEOUS FRACTURES OF THE FEMORAL NECK AFTER THE INTENSIVE IRRADIATION OF CARCINOMA OF THE UTERUS

by

G. Kok

Between 1941 and 1950, eight hundred and ninety-six patients were treated in the Rotterdam Institute of Radiotherapy for carcinoma of the uterus by irradiation of the true pelvis. The patients comprised six hundred and fifty-two with primary carcinoma of the cervix or body of the uterus and two hundred and forty-four irradiated after operation or for recurrence. Spontaneous fracture of the femoral neck occurred in thirteen cases (1.45 %). Varying percentages of the incidence of this complication are found in the literature, *e. g.* DALBY, JACOX and MILLER: 2.1 %, and STAMPFLI and KERR: 0.87 %. MILLER and FOLSOME (Michigan Univ.) reported the high incidence of twenty-five cases out of six hundred and seventy-six cases of carcinomas of the cervix treated. MCCRORIE described ten cases in eleven hundred and ninety-seven patients but gave no percentage as, according to him, a number of cases were certain to have been overlooked.

The division of our patients according to age was as follows:

Table I

55 yrs	55—59	60—64	65—69	70—74	75—79
1	3	4	2	0	3
40 yrs	55, 56, 57	61, 64 62, 64	68, 69		75, 75, 77

Average age about 63 years.

Comparable reports from the literature are DALBY et al.: fourteen cases, average age 57 years; REGGIO and WILSON, average age 63 years;

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STAMPFLI and KERR: 55 years. Of the twelve cases of the last-mentioned authors, one patient was 37 and one 34 years old. All the others were over 55.

The 40-year-old woman who was treated in our Institute received, exclusively to the left half of the pelvis, a dose of irradiation which was relatively very high. She had a large post-operative recurrence at that site and for this reason could not be included in our scheme of routine treatment. From the above, the conclusion is justified that, with the ordinary irradiation techniques, the fracture generally occurs in older women. Bilateral fractures were seen in five out of thirteen cases; besides the femoral fracture, bony damage in the form of a fracture of the true pelvis was observed twice.

In this connection it was also striking that the left femur was fractured much more often than the right and that in five bilateral cases the left femur became fractured first in three instances. In the literature, only STAMPFLI and KERR have reported this observation.

It cannot easily be explained why only one femur should become fractured in spite of the application of the same dose to both sides of the pelvis. MCCRORIE considered that postural asymmetry might be a factor. This seems not improbable in view of the fact that in five patients in whom both the left and the right femur were fractured, these two complications occurred more or less concomitantly in only one case.

The thirteen patients may be classified according to the nature of the condition they presented at the beginning of treatment:

One case: Carcinoma of the cervix, operated on, with recurrence: a large part of the left half of the pelvis was filled by a tumorous infiltration.

One case: Carcinoma of the uterine body without infiltration into the parametrium.

One case: Carcinoma of the uterine body, radically excised.

Ten cases: Carcinoma of the cervix. Stage I — 1 case.
Stage II — 6 cases.
Stage III — 3 cases.

As far as the case descriptions in the literature permit of conclusions, practically all patients were in Stage II or worse when presenting themselves for treatment.

The period elapsing between the beginning of treatment and the occurrence or diagnosis of the fracture appears to vary fairly widely. This is what might be expected (see below) and is in agreement with the literature. The fact that all patients may complain of pain in the

affected hip some considerable time before the fracture occurs, is of great importance. In general, in women between 50 and 70 years of age, this symptom arises about one year or more after treatment. The period of complaints of pain before the fracture occurs varies greatly in length, which is, of course, not astonishing as it is influenced by many factors.

As a first symptom of an impending fracture the patient often mentions pain in the groin, sometimes also in the knee. I consider as an important early symptom the fact that the patients start to 'rest' the affected hip, because a slight impairment of function occurs early. It is noticeable that the patient walks with some care. This sign is not, however, pathognomonic of this complication, because it may also be observed when there are bone metastases in the lumbar spine, pelvis or lower extremities; when a carcinoma of the breast is present for instance, it is often an early sign of skeletal metastases in these regions. Pain in the posterior part of the hip or in the leg are also sometimes mentioned. In the earliest stage, there is often very little found wrong with the hip but if one keeps this complication in mind, however, rotation will almost always be found slightly impaired and painful. As the patients generally belong to the older age groups, radiography of the pelvis will often show signs of arthrosis, and the diagnosis of arthrosis deformans has often been made. As a consequence, patients have sometimes been given still more irradiation to the affected joint. In the later stages, when the fracture has occurred, there is, of course, considerable impairment of movement and the patient limps. The characteristic roentgen appearances of a spontaneous fracture are then usually present (Fig. 1).

Our cases appear in general to have had somewhat medially situated fractures of the neck (subcapital fractures) with upward displacement of the shaft. From the roentgenograms illustrating McCrorie's article, it would appear that most of the fractures in this author's cases were nearer the middle of the femoral neck. It is remarkable that the fracture line is generally hazily demarcated with slight to considerable sclerosis of the bone structure at the site of fracture. Studies of operation specimens showed that the fracture zone consists of compressed atrophic trabeculae and fragmentation, occasionally combined with bone regeneration, so that some cohesion often still existed between the main fragments. The bone was also very brittle in the fracture region. This is in accord with cases from the literature and explains the roentgenographic appearances.

In an earlier stage, just before the fracture occurs, roentgenograms shows a zone of irregular bone condensation in the femoral neck (Fig. 2). If the patient has previously received intensive irradiation to the region

Fig. 1. Spontaneous fracture of the femoral neck following irradiation.

Fig. 2. Irregular bone condensation in the femoral neck indicating an incipient fracture.

of the true pelvis, this is practically conclusive of an incipient fracture. Existing local injury to the trabeculae offers a probable explanation. The appearances recall the so-called "Loosersche Umbauzonen", which have been described in cases of avitaminoses at this age, but an early diagnosis of impending fracture is usually justified. Unfamiliarity with these radiologic signs will probably lead to a spontaneous fracture due to metastases being first considered. It has, however, been observed that metastases from a uterine carcinoma, contrary to those from a mammary carcinoma, only very seldom occur in the femoral neck. The true nature of the signs may often be recognized only after a considerable period as the fracture develops but slowly and takes some time to become complete. In this connection, McCRORIE stresses the fact that the pain is too often supposed to be metastatic in origin and that this constitutes one more reason why the true nature of the fracture may go unrecognized. The sometimes chronic, lingering character of the pain adds to this difficulty.

The fact that the fractures are often relatively remarkably painless has been ascribed by KULSING and HANSSEN to the devitalization of the periosteum caused by the irradiation. In my experience, however,

the pain complained of is generally severe even in the stage when the roentgenograms shows no fracture.

Dosage and irradiation technique

The purpose of external roentgen irradiation in the treatment of uterine carcinoma is to increase the dosage to the lateral part of the parametrium and near the pelvic walls where there are important regional glands; because of its rapidly diminishing intensity, radium irradiation decreases strongly in the lateral directions. The lateral part of the parametrium lies very close to the head of the femur and, however accurate the technique, it is practically impossible to avoid the head completely if one wishes to be sure of an adequate dosage to this part of the pelvis with its regional glands. It has been demonstrated, however, that with the irradiation techniques applied, the femoral neck also received a heavy dose.

Eleven of the twelve patients were treated between 1942 and 1949 with the same irradiation technique, consisting of an anterior field of 18 × 18 cm bisected by a lead strip 3—4 cm wide, a posterior field of the same size and right and left lateral fields of 15 × 15 cm with the central beam directed towards the parametrium, *i. e.* traversing both the femoral head and neck. These fields mostly received a dose of 2,000 r measured in air, divided into two series of 1,200 and 800 r respectively, at six weeks' interval.

The initial opinion of many authors, *e. g.* KROPP, ZOLLNER, BAENSCH, PHILIP, TRUELSEN and also held in our Institute, was that the lateral fields were the chief cause of the heavy irradiation doses to the femoral head and neck.

BACLESSE, DALBY, JACOX and MILLER used only anterior and posterior fields. The last three authors, however, observed fractures of the femoral neck in 2.1 % of cases. Measurements carried out in co-operation with SOMERWIL, physicist of the Institute, and using a phantom of a female pelvis of average size in water, showed that with the above irradiation technique the head and the medial part of the neck of the femur are liberally exposed to irradiation through the posterior and anterior fields (18 × 18 cm), assuming an average circumference of the patient. With a dose of 2,000 r measured in air on the skin fields as described above, the following values were determined by means of a small electron-ionization chamber:

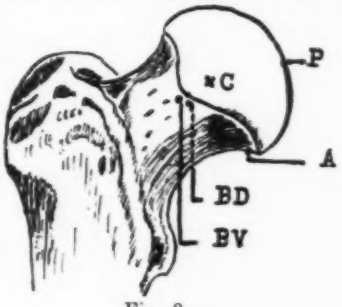


Fig. 3.

Table II

	From all fields:	From ant. and post. fields only:
1. Centre of the head (point C)	3,200 r	1,720 r
2. Deepest point of the acetabulum at the attachment of the ligamentum teres (point P)	3,400 r	2,020 r
3. Most medial part of the neck, viz. just in front of the bone-cartilage interface of the head.		
A — caudally	4,100 r	2,080 r
BV — anteriorly	4,000 r	2,180 r
BD — posteriorly	3,600 r	1,500 r

In spite of the accuracy of the measurements these are still more or less relative figures, because, according to WACHSMANN, living bone absorbs more radiation than the cleaned, *i. e.* macerated, bone generally used in phantom measurements. In this cleaned bone, the soft parts and the marrow have largely been replaced by air. By immersing the phantom in water before the measurements, most of the air in the marrow cavities will be replaced by water, thus rendering the condition more or less as in vivo.

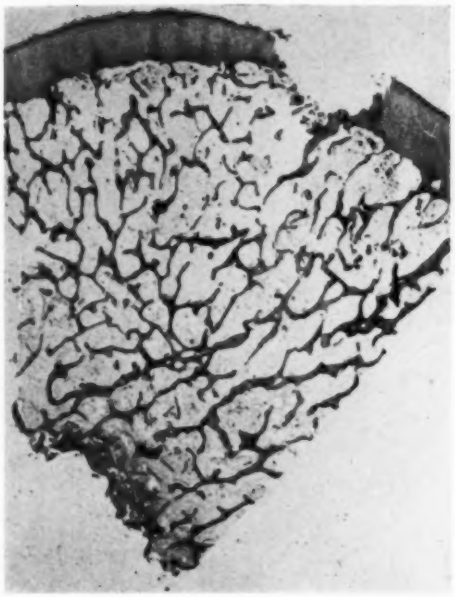
It appears that the centre of the head receives the lowest dosage, especially as compared to the surface of the medial part of the neck which with this technique is also covered by the anterior and posterior fields.

In connection with these phantom measurements, the morbid anatomy report on two femoral heads removed operatively is interesting.

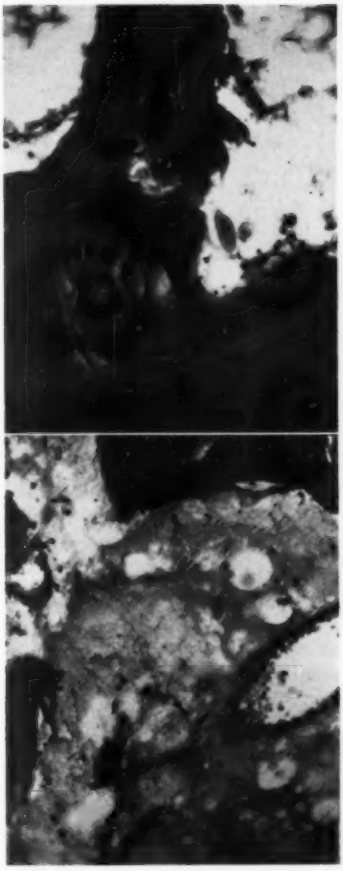
The femoral head of the first case showed the following histologic appearances (WIJERS):

The cartilage of the head is completely intact (Fig. 4 a); the bone tissue situated beneath it, the extremely thin bone layer as well as the trabeculae, are markedly atrophic, most of the cells being necrotic or at any rate unstainable (Fig. 4 b). In the interstices between the trabeculae there is much fatty tissue containing an exudate of mostly plasma cells. No osteoblasts or osteoclasts are to be found near the trabeculae (there is certainly no predominance of osteoclasts as described by DAHL (1936) in animal experiments in which the osteoblasts proved more sensitive to irradiation than the osteoclasts).

In the deeper-situated tissue the fat cells have become widely separated by protein-containing fluid (Fig. 4 c) producing a protein-rich oedema. In this oedematous fatty tissue, between the trabeculae, no pronounced changes of the vascular walls are observed, but there is considerable dilatation of the veins, causing stasis or at any rate a very slow rate of flow, so that a disturbance of the circulation may be assumed to have existed. The trabeculae have a similar appearance as directly beneath the cartilage. Still deeper they become more numerous and larger again, and gradually regain normal cell-stainability; here and there they show the so-called 'mosaic structure'.



a.



b and c.

Fig. 4 a. Microscopic specimen showing intact cartilage of the femoral head.

b. Atrophic bone with necrotic cells beneath the cartilage.

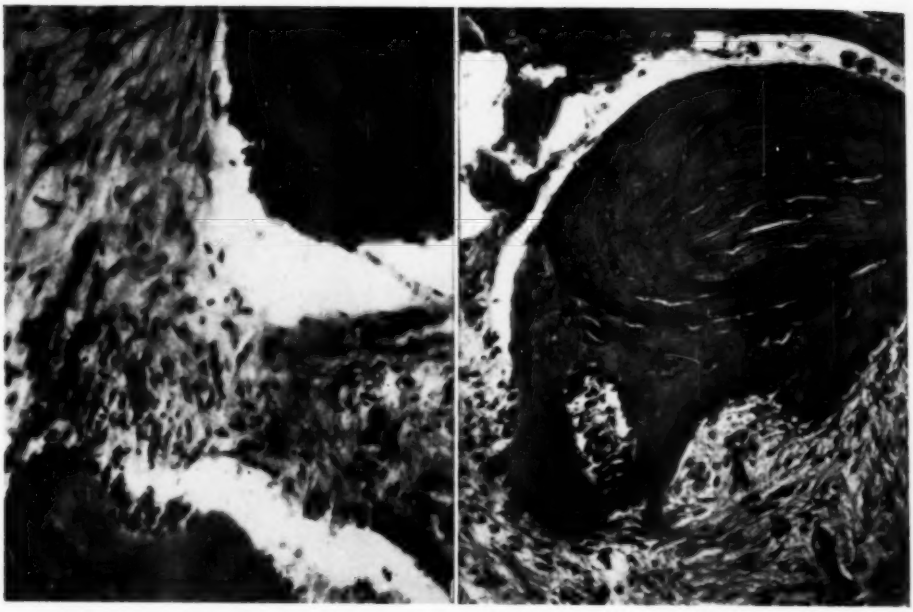
c. The fat cells have become widely separated by protein-containing fluid.

Fibrous marrow is found between the trabeculae with infiltration of a considerable number of plasma cells.

Simultaneously with the fibrous marrow osteoblasts are seen to reappear, now and then numerous, and in small areas forming new bone around old trabeculae. Small newly-formed trabeculae with osteoid border-zones are also observed (Fig. 5 a, b).

There is some resemblance to osteitis fibrosa, as described by TRUELSEN (1942). These regions will, however, have bordered the fracture surface and it is difficult to assess the influence of this fact on the histologic picture. Some of the new trabeculae resemble newly-formed callus, but the structure is more irregular.

In the articular capsule small-celled infiltrations are seen, as well as slight swelling of the intima and thickening of the adventitia of a few small blood vessels (Fig. 5 c).



a. b.

c.

Fig. 5. a and b. Fibrous marrow osteoblasts. Newly-formed trabeculae with osteoid border zones.

c. Small-cell infiltration of the articular capsule.

The second femoral head removed by operation showed the following microscopical appearances:

The cartilage has a somewhat fibrous surface, possibly due to an artefact. The fovea shows no changes from the normal. Under the cartilage a relatively thin corticalis is found, certainly shallower than usual. Beneath it, there is a very wide structure of trabeculae, the cells of which have remained stainable, as have the cortical cells. There are no osteoblasts or osteoclasts in the region of the trabeculae or the under surface of the corticalis. The fatty tissue in several situations between the trabeculae seems necrotic in having unstainable nuclei. In the deeper layers the fatty tissue gradually becomes oedematous and in certain areas contains erythrocytes and a few exudate cells, among them plasma-cells; a few osteoblasts are seen to occur here and there. Still deeper there is fibrous bone marrow and a great many osteoblasts; a few scattered giant cells are seen in the connective tissues. A number of necrotic bone fragments, distributed in an irregular pattern, are found in this region. A few very small areas of callus are present. The irregularity of the lower zone of demarcation is probably due to the fact that the fracture remnants and callus are intermingled.

To summarize, we find, in the main, the same changes as in the first femoral head, although somewhat less clear.

In the tissue removed from the fovea capitis no important changes of a definitely pathologic nature were seen.

The microscopic changes in cases of fracture of the femur after irradiation as described in the literature are not constant; this is not surprising, as the ages of the patients differed and the irradiation techniques and dosages used were not the same. Investigators such as BAENSCH, DALBY, TRUELSEN, OEKRAINETZ, BILLER, STAMPFLI and KERR, however, also mention the occurrence of osteoporosis. Vascular changes such as sclerosis and parietal thickening have been described by DALBY, OKRAINETZ, and BILLER; TRUELSEN however, saw no particularly striking vascular damage, but calls attention to the remarkable paucity of bone cells. STAMPFLI and KERR state correctly, I think, that clearly visible vascular changes do not always have to be present, because the dosage to the femoral neck does not have to be nearly so high as, for instance, to the jaw in irradiation of intra-oral carcinoma.

A knowledge of the vascular supply of the region is essential if we are to arrive at a conclusion concerning these spontaneous fractures. According to the studies of WOLCOTT and TUCKER, LOGROSCINO and many others, the upper part of the femur has three vascular supplies, viz. the nutrient artery of the shaft, the retinacular (or capsular) arteries and the foveal artery or arteria ligamenti teres.

Most important of the three are the retinacular arteries, which have their origin in the arteria circumflexa. They are divided into three groups — the posterior-superior, posterior-inferior and the anterior, of which the first constitutes the main group.

The retinacular vessels lie loosely under the synovial membrane. In their course along the femoral neck they give off many very small

branches which pass via the periosteum through the narrow Volkmann's canals of the compacta and anastomose with the nutrient artery of the shaft. The superior vessels especially are very numerous. When the vessels reach the cartilaginous roof of the head they have become much more fixed. The vessels of the posterior-superior group cross the bone-cartilage interface and then travel towards the centre of the head.

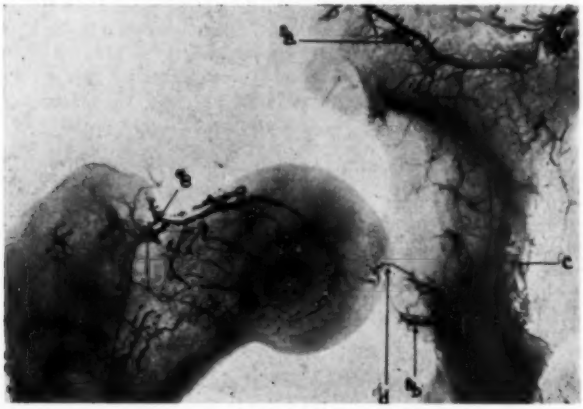


Fig. 6. Arterial pattern of the femoral head (after LOGROSCINO).

The studies of TUCKER and WOLCOTT have also shown that the foveal arteries of the ligamentum teres increase in size with increasing age, so that in middle age a considerable part of the vascular supply may come from these vessels. CHEYNEL demonstrated, with the aid of prepared specimens of the vascular supply system of the hip, that in senescence the vascular supply is markedly diminished and only the posterior-superior group remains available. Consequently, the vascular supply of the femoral neck is largely dependent on the narrow vessels given off by the retinacular arteries which penetrate the compacta through the Volkmann's canals. In phantom measurements it was demonstrated that it is this surface, with the periosteum covering it, which is exposed to a relatively heavy dose of irradiation. It has been proved by EWING (1926) and others, by means of microscopic preparations, that the periosteum, which lies freely against the bone, is particularly sensitive to irradiation. When its tolerance is exceeded it begins to swell, while the inner layer, which is in contact with the bone, is changed into a thick hyaline layer without cells (the osteoblasts disappear). If this happens, the periosteum often becomes separated from

the bone, thus also disturbing its chief source of nutrition. Moreover, the intricate system of the Volkmann's and Haversian canals as well as the cells in the bone lamellae are also considerably affected owing to the large amount of secondary radiation from the bony tissue, which contains 85 per cent of calcium (atomic weight 40).

EWING believes that the bone cells are destroyed first, both by direct influence of the irradiation and by impaired nutrition owing to obstruction in the narrow vascular systems of Havers and Volkmann. It seems likely that in the compacta region of the femoral neck, moderate damage to the periosteum and changes in the multiple small vessels passing through the Volkmann's canals would suffice to cause considerable disturbances of circulation or nutrition in this region. One can imagine how the bone cells in the compacta region of the femoral neck become more or less heavily damaged by the direct influence of the rays and are soon afterwards further injured by the occurrence of diminished nutrition as a consequence of impaired circulation. This is in accordance with the histologic appearances. In the compacta region, the bone cells become necrotic and there is no longer either osteoblastic or osteoclastic activity. According to MCCRORIE the venous dilatation present in this region also causes the Volkmann's and Haversian canals to dilate, which is often concurrent with absorption activity. Indeed, we see many plasma cells in this region. However that may be, the trabeculae are devitalized and very atrophic, just in the region which has to bear the most weight, so that a fracture may readily occur. The femoral head itself is not so liable to fracture, as it is protected by the firm cartilaginous roof, which has not undergone much change. The process will take some time, and it is not surprising that this period is shorter in older individuals as in these the vascular supply is decreased, as demonstrated by CHEYNEL, and the vulnerability of the bone cells increased. SLAUGHTER has stressed that a more or less pronounced osteoporosis may also exist (senescence osteoporosis).

In all our three patients over 70 years of age, the fracture occurred after a shorter period than in most of the younger patients. Moreover, only one of them (75 years old) received the customary irradiation dose, while the other two were given considerably less.

It was demonstrated with the arterial preparations of TUCKER and LOGROSCINO that the end-branches of the posterior-superior group of retinacular vessels, which proceed towards the centre of the head, are of considerably larger calibre than the tiny vessels which this group of arteries gives off for the supply of the femoral neck (Fig. 6). Consequently irradiation will influence these vessels to a much lesser degree and the vascular supply of the centre of the head will remain more intact. Moreover, the dose of irradiation in this region is lower. This might

Fig. 7. Callus formation and commencing bone union after a spontaneous fracture.

explain the histologic finding that in the deeper layers one sees living bone cells and regeneration, though the latter is somewhat atypical. Further, the artery of the ligamentum teres may have a supplementary function in individuals of average age. This may be the reason why, if the displacement is not too marked, the fracture heals so well. The fracture probably occurs only in those cases in which regeneration has not been able to keep up with the degenerative absorption, an assumption which is corroborated by the fact that pain affecting the hip in irradiated patients often disappears spontaneously after some time.

The most striking illustration of this assumption is the case of a woman of 40, one of the series of cases mentioned, who was given an extremely high dose to the left half of the pelvis (Table II) and in whom the fracture healed completely with only slight deformity.

Case 1. A patient, aged 40 was admitted with a large tumorous infiltration in the left iliac fossa, adherent to the pelvic wall, as a recurrence of an extirpated cervical carcinoma.

Irradiation to the left half of the pelvis by three fields — anterior, posterior and left lateral. Dose: 1,600 r. per field in 4 weeks and six weeks later a second series totalling 800 r. per field. Twenty-one months after the last irradiation there was again

resistance and pain on pressure in the left iliac fossa. Irradiation of the same three fields with a dose of 1,400 r. per field was repeated.

October, 1946. Ten months after the third series the patient had sharp pain in the left leg on walking. Examination showed that the infiltration was no longer marked. Pelvic roentgenograms: no definite changes.

December, 1946. Considerable pain in the left leg.

January, 1947. Pain now less after rest.

Roentgen examination: In the border-zone between head and neck of the left femur a few ill-defined rarified areas and a sclerotic streak indicating a fracture.

July, 1947. Pain steadily decreased. There was still a clearly visible sclerotic streak below the head but no longer any rarified areas. Callus formation with union inferiorily. Slight varus position (Fig. 7).

February, 1951. Nothing further to report.

Fig. 8. Fracture of the superior ramus of pubic bone associated with a fractured femur.

The favourable course in this relatively young patient was doubtless due to the good vascular supply present at this age. Fracture of one of the pelvic bones in conjunction with a fracture of the femur will occur less frequently when using the same irradiation technique, because generally the forces acting on these parts of the skeleton are less concentrated and the vascularization is probably different. In our case series of thirteen fractured femurs there were two which also showed a fracture of the superior ramus of the pubic bone (Fig. 8).

The prognosis of a spontaneous fracture of the femoral neck after irradiation appears favourable. In those of our patients who were not operated on and in whom the displacement was not too great, good consolidation always resulted. It usually proved impossible to reduce the displacement existing because in most cases in which the fracture had been present for some time, the fragments had already begun to grow together. For this reason, considerable deformity has remained in several cases.

In the future, attention must be focussed on the prevention of the complication of a spontaneous fracture. To achieve this, roentgenographic control of the course of the radiation beams is necessary. Doubtless, this will reduce the incidence to a minimum. If one wishes to be sure, however, of administering an adequate dose to the lateral walls of the true pelvis, which may be vital to the patient, the remaining small risk will have to be taken.

The therapist familiar with this complication will generally be able to prevent, however, an impending fracture. In consultation with an orthopaedic surgeon measures should be taken to immobilize the patient immediately and to relieve temporarily muscular activity as much as possible; for this purpose, a plaster cast to the pelvis may be useful. The period of immobilization should be at least three months. Complaints of pain, signifying that adequate union has not occurred, indicate further immobilization; in the meantime, care should be taken to improve the general condition as much as possible.

Case 2. A patient, aged 68, was treated towards the end of 1950 with roentgen rays and radium for carcinoma of the cervix, Stage II. On re-examination at the beginning of October 1952, she complained of pain in the right knee and upper part of the leg. It was noted that she walked with difficulty and avoided strain on her right leg. A gynaecologic examination revealed no signs of recurrence. Adduction and rotation of the right hip were painful.

November, 1952: A roentgen examination showed areas of increased density in the medial part of the neck of the right femur; a fracture was uncertain. The patient was immobilized (plaster cast) and given Vitamin D injections. December, 1952: Pain had almost completely disappeared and the patient walked practically normally. Roentgen examination: no essential change since November. January, 1953: No symptoms; patient walked normally.

When a spontaneous fracture has nevertheless occurred, one is faced with the choice between conservative and surgical treatment. Close cooperation with an orthopaedic surgeon is, of course, imperative. Which of the two methods is to be employed depends among other things on the patient's age and general condition. Before deciding upon surgical intervention, due consideration will have to be given to the condition of the carcinomatous growth. Conservative treatment has its own well-

known contra-indications — the risk of thrombosis, hypostasis etc.; the renal condition will also have to be taken into account.

As regards surgery, I consider that a Smith-Petersen-Johansson osteosynthesis should be excluded for the following reasons:

1. During the acute stage, the metal pin will doubtless do still more damage to the vascular supply in the vulnerable region of head and neck and increase the risk of necrosis. Moreover the pin would have to be inserted into a region in which the trabeculae are very much atrophied.
2. If there is considerable displacement of the fragments, the risk of necrosis becomes still greater as rupture of the last main distal nutrient vessels disturbs the blood supply to the head still more (OOSTERHUIS).

Though its long-term results remain to be judged, JUDET's operation, in which the fractured head is replaced by a plastic one, seems to offer possibilities. Whether this operation is possible depends on the condition of the bone of the distal part of the femoral neck. It has been performed so far in two patients with spontaneous irradiation fractures. One of these patients died from progression of the carcinoma. The other patient, in whom arthroplasty was done over a year ago, has still considerably impaired hip function, but is able to walk reasonably well. Control radiography after one year showed good repositioning of the hip. The acetabulum, however, was somewhat irregular and atrophic.

SUMMARY

Irradiation techniques for carcinoma of the uterus in which the femoral neck is traversed by part of the rays, involve the risk of spontaneous fracture of the neck occurring after some time in a certain percentage of the older patients. Improvement of irradiation technique may largely prevent this complication. Pain may exist for a considerable length of time before fracture occurs. This makes it possible in many cases to avoid fracture by diagnosing the condition in time and treating it conservatively; the prognosis is then favourable.

ZUSAMMENFASSUNG

Bestrahlungsmethoden beim Uteruskrebs, bei denen der Oberschenkelhalsknochen von einem Teil der Strahlen durchquert wird, bringen in einer gewissen Prozentzahl der älteren Patienten nach einiger Zeit die Gefahr des Auftretens einer Spontanfraktur des Schenkelhalses mit sich. Verbesserungen der Behandlungstechnik können diese Komplikation weitgehend verhindern. Schmerzen können geraume Zeit vor dem Auftreten der Fraktur vorhanden sein. Dies macht es in vielen Fällen möglich, eine Fraktur durch rechtzeitige Diagnose des Prozesses zu vermeiden und diese konservativ zu behandeln. Die Prognose ist dann günstig. Die pathologische Anatomie wird besprochen und eine Theorie bezüglich der Pathogenese entwickelt.

RÉSUMÉ

Les techniques d'irradiation pour cancer de l'utérus dans lesquelles le col du fémur est traversé par une partie du rayonnement entraînent un risque de fracture spontanée du col survenant au bout de quelque temps chez un certain nombre des malades les plus âgées. Le perfectionnement de la technique d'irradiation peut dans une large mesure prévenir cette complication. La douleur peut précéder de beaucoup la fracture. Ceci permet d'éviter dans de nombreux cas la fracture grâce à un diagnostic fait en temps utile et à un traitement conservateur; le pronostic est alors favorable. L'auteur étudie l'anatomie pathologique et propose une théorie pathogénique.

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BOOK REVIEW

X-Ray Sieve Therapy in Cancer. A Connective Tissue Problem. By Benjamin Jolles. 192 pp., 51 ill. H. K. Lewis & Co. Ltd., London 1953. 25 shillings.

In this book, the author presents his theories and practical experiences in 'roentgen sieve therapy' which he has employed since 1941. He points out the great importance of the connective tissue in the isolation and destruction of tumour cells and describes, in part, certain new results in the research into its histology and biochemistry.

The radiosensitivity and radioresistance of the cells depend, according to the author, in the first place upon the power of reaction of the healthy tissue which surrounds the tumour.

The author sees a possiblility, peculiar to the sieve method, of sparing the healthy tissue to a large degree but at the time the opportunity of giving a large tumour dose by reason of the fact that the method considerably increases the skin tolerance dose.

The author makes interesting studies in direct and indirect radiation effects in the experimental treatment of cancer of the skin.

In the assessment of the indirect radiation effect on the skin, however, it is sometimes difficult to accept the author's views. The skin doses he applies to the areas covered by the sieve, lie rather low compared with those of other authors and his own published isodoses. The radiation effect on the skin is, as a matter of fact, not only caused by the surface dose but also by the volume dose on the tissue situated just below the surface. For this reason, certain apparent changes between the physical dose and the biological effect could, in the reviewer's opinion, be explained in a simpler way. Since 1945 the author has treated 54 patients by means of various chess-board-like lead sieves and in this way has developed his own methods of treatment.

The late results are not yet sufficiently known to make conclusions possible, and the author therefore reserves the method only for special cases. He sees in the heterogeneous distribution of the doses, also present in brachyradium treatment, a favourable factor for the healing power of the tissues and he prefers the former to the use of the homogeneous beam. He recommends hard radiation, small fields and a tumour depth which preferably ought not to exceed 12—15 cms. He issues a warning against a multiple-field technique, which by cross-fire eliminates the principle of the promotion of healing associated with the sieve technique.

The book can be recommended to every radiologist engaged in sieve therapy, especially as this is the first comprehensive work of its kind. The author has had many years' experience and brings forward a number of fresh suggestions, even though certain biologic problems remain unsolved.

Gustaf Notter